

Great Health Myths Exposed



Foreword

by Michael Gurr, PhD

Whether diet plus plays a major role in heart disease is a question that interests us all. Author Ravnskov has a mission. To inform his readers that there is a side to this question other than the view usually presented to us.

Government and health authorities never tire of remaining those of us who live in industrialized countries that heart disease is a major cause of death. They go further and tell us that heart disease is eminently preventable.

While conceding that genetic background interacts with numerous environmental factors to influence each individual's risk of succumbing to heart attack, they insist that diet is foremost among these factors as a cause of heart disease, and that modifying diet provides a straightforward means of preventing heart attacks. If only people would do what they are advised—reduce their intake of fats, especially those rich in saturated fatty acids—then the high toll of death and disability from this disease could be readily reduced. If only!

What is the scientific basis on which this advice is based? Although the many reports of “expert committees” acknowledge that diet may influence the underlying pathology of heart disease in several ways, current “dietary guidelines” are based mainly on what Dr. Ravnskov calls “the diet-heart idea.” Greatly simplified (which it normally is!), this idea proposes that dietary fats rich in saturated fatty acids raise the concentration of cholesterol in the blood. This in turn is involved in the initiation of arteriosclerosis, which through its restriction of blood flow to the myocardium and its tendency to generate thrombi, leads to myocardial infarction.

Dr. Ravnskov's contention is that the diet-heart idea is built on sand. He leads us through the history of the concept in an interesting and readable way. His writing clearly demonstrates the enormous depth and range of his reading on this subject. Step by step he examines the evidence for the diet-heart idea, and step by step he shows us how that evidence may be flawed and contradicted by other research that is rarely acknowledged and quoted.

Medical science has generally been highly regarded by the public, who have rarely questioned its findings because it is perceived as helping to improve mankind's lot. It will come as a surprise to many readers to learn how many studies of diet and heart disease were poorly designed and conducted, how many did not produce the results that have been claimed for them and have been quoted irrelevantly or misleading, and how many published studies exist whose results seriously question or contradict the diet-heart idea but are never acknowledged or quoted. Some of these tactics are not only misleading but also sometimes amount to scientific fraud.

Dr. Ravnskov is well qualified to write such a book. He is a general practitioner who regularly needs to advise patients who have heart disease or who are worried that they might have it. The book begins with an insight into problems of one such patient, an otherwise healthy woman who began to worry after a company health screen revealed that she had high cholesterol and who was told by the company medical officer that she might have a heart attack in five years if she didn't do anything. Dr. Ravnskov and many like him are concerned that public health messages based on poor science may not only be ineffective but also may cause unnecessary worry to people who were previously free of health cares.

As well as conducting his medical practice, Dr. Ravnskov is also a scientist who has published a number of papers, including some penetrating analyses of the diet-heart literature. He is one of a growing number of scientists who have found what they have read disconcerting.

Why do we hear so little about this alternative view? Few scientists seem willing to stand up and question what has been accepted dogma? Dr. Ravnskov lists a few at the end of his book and outlines their views and credentials. Most are, like the author, individuals with inquiring minds who are not directly involved in heart disease research. Some, however, have been eminent researchers into heart disease; their firm stand against conventional has often alienated them from the establishment community. By contrast, many who support the consensus view have made their reputations in this view, have been supported by research grants often amounting to millions of dollars and have a vested interest in continuing to support and sustain the diet-heart idea.

Another dimension is this story that Dr. Ravnskov discusses is the approach to lowering cholesterol by drugs, which has almost always been more effective than diet. The cholesterol story, therefore, has the backing of the multimillion-dollars drug industry. While this backing is not reprehensible to itself, the distinction between the ability of drug and dietary treatment to lower blood cholesterol has often become so blurred that lay people are frequently confused into believing that dietary modification could achieve exactly the same effect as drug treatment when it clearly cannot. Alternatively, many may be persuaded that they need drugs when clearly they do not.

Quite apart from showing us the flimsiness of the scientific evidence upon which dietary advice to prevent or reduce heart disease is based, Dr. Ravnskov also addresses an even more serious problem. Could attempts to reduce cardiovascular mortality by lowering blood cholesterol actually do harm? Several authors have reflected that it might and have cited the evidence. To this end, Ravnskov discusses the worrying observation that even when cardiovascular deaths have been reduced in some intervention trials, subjects died of other causes—sometimes cancer, sometimes suicide or other forms of violence—resulting in no overall change in death rate. Many “expert” committees reviewing this evidence have tended either to ignore this phenomenon or have argued that it can safely be disregarded, but the admonition “do no harm” comes back to haunt us.

Many with establishment views will regard Dr. Ravnskov as a crank. That would be a grave mistake. He has done his homework, he is not a lone voice in the wilderness, and he deserves to be taken seriously. Above all, this book will make us all think more deeply about the true role of diet in heart disease and about the quality of the information that we receive.

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Author's Foreword

When the cholesterol campaign was introduced in Sweden in 1989 I became much surprised. Having followed the scientific literature about cholesterol and cardiovascular disease superficially I could not recall any study showing a high cholesterol to be dangerous to the heart or the vessels, or any type of dietary fat to be more beneficial or harmful than another one. I became curious and started to read more systematically.

Anyone who reads the literature in this field with an open mind soon discovers that the emperor has no clothes, and so did I. But I also learned that the critical analyses or comments, that I sent to various medical journals, were most often met with little interest from the editors and mocking answers from the reviewers. Besides, the inaccuracies, the misinterpretations, the exaggerations and the misleading quotations in this research area were so numerous that to question them all demanded a book.

The first edition was published in Sweden 1991 and in Finland 1992. The books made little impact. In Sweden the science journalists usually lost their interest in the subject when they, after having read the book, consulted the researchers or health authorities that I had criticised. In Finland the book was put on fire in a television show on channel 2 after having been belittled by some of the Finnish proponents to the cholesterol campaign.

The uncritical introduction of the cholesterol campaign in Sweden was most probably due to its promotion by large American health and research institutions such as the National Heart, Lung and Blood Institute and the American Heart Association and their influential members. Evidently, the Swedish health authorities must have thought that such prestigious authorities could not be wrong. But Sweden and Finland are small countries. I thought that, maybe I could reach more critical and independent journalists and researchers by publishing the book in English. Several years of searching among editors and literature agents was unsuccessful, however; the book was considered of no commercial interest.

With the advent of internet I saw a way to inform the public and in 1997 I published selected sections of the book on the web. According to the search engine Direct Hit my website soon became one of the top ten most popular

sites about cholesterol and from email letters I learned that many laymen and researchers were just as skeptical to the cholesterol campaign and the diet-heart idea as I, or at least they became skeptical after having read my website. One of the responders was the author and publisher of Nourishing Traditions, Sally Fallon. As an academic nutritionist she had reached to similar conclusions as I and asked if she might publish my book.

All researchers are standing on the shoulders of their predecessors and so do I. Hopefully, I have paid credit to most of them in the book. But there are other important individuals that have contributed to this book in some way or another. First of all I would like to thank Bodil Jönsson and Olof Holmqvist for their many ingenious comments to the first draft. I am also greatly indebted to Linda Newman for her tremendous and unselfish work changing my first, broken translation of the Swedish edition to good English. At a later stage, when I had destroyed some of Linda's good work by updating and revising the text, Sally Fallon repaired the damage. I would also like to mention here Lars Werkö who has given me invaluable support and encouragement through the years.

The following individuals have been important in various ways, either by giving me valuable, critical comments to the various drafts or simply by showing me their qualified appreciation of my work. The list includes, in alphabetic order, Poul Astrup, Jonas Bergström, Christer Enkvist, Michael Gurr, George Mann, James McCormick, Peter Nilsson-Ehle, Robert E. Olson, Eskil Richardson, Ray Rosenman, Kari Salminen, the late Petr Skrabanek, Lars Söderhjelm, and Nicolai Worm.

Last, but certainly not least, this book would never have been written without the patience and encouragement of my wife Bodil.

Introduction: The Diet-Heart Idea: A Die-Hard Hypothesis

The great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact.

Thomas Huxley (1825-1895)

Did you know...

- Cholesterol is not a deadly poison, but a substance vital to the cells of all mammals?
- Your body produces three to four times more cholesterol than you eat?
- This production increases when you eat only small amounts of cholesterol and decreases when you eat large amounts?
- The “prudent” diet, low in saturated fat and cholesterol, cannot lower your cholesterol more than a small percentage?
- The only effective way to lower cholesterol is with drugs?
- The cholesterol-lowering drugs are dangerous to your health and may shorten your life?
- The cholesterol-lowering drugs, called statins, do lower heart-disease mortality a little, but this is because of effects other than cholesterol lowering? Unfortunately, they also stimulate cancer.
- You may become aggressive or suicidal if you lower your cholesterol too much?
- Polyunsaturated fatty acids, those which are claimed to prevent heart attacks, stimulate infections and cancer in rats?
- If you eat too much polyunsaturated oil you will age faster than normal? You will see this on the outside as wrinkled skin. You can’t see the effects of premature aging on the inside of your body, but you will certainly feel them.
- People whose blood cholesterol is low become just as atherosclerotic as people whose cholesterol is high?
- More than thirty studies of more than 150,000 individuals have shown that people who have had a heart attack haven’t eaten more saturated fat

or less polyunsaturated oil than other people?

- Old people with high cholesterol live longer than old people with low cholesterol?
- High cholesterol protects against infections?
- Many of these facts have been presented in scientific journals and books for decades but proponents of the diet-heart hypothesis never tell them to the public?
- The diet-heart idea and the cholesterol campaign create immense prosperity for researchers, doctors, drug producers and the food industry?

A sorry story

Karla didn't know it.

Karla and I live in the southern part of Sweden, a prosperous country where nobody needs to starve. If anything, overweight is a problem for many people.

In Sweden people grow old; the people of Sweden enjoy one of the longest life spans in the world. Therefore, heart disease is a common cause of death simply because heart disease is a disease of old age. But man is never satisfied, and great efforts are made to prolong life. One of these efforts is to determine which people have high cholesterol because scientists say that lowering cholesterol may prevent heart disease and give you a longer life. When you have read this book you will know that nothing could be more wrong. But first let me tell a little more about Karla.

Karla has been my patient for several years. On her occasional visits, she had always been cheerful and optimistic.

Now she is tired and depressed, not at all the way she used to be.

Karla is sixty-two. She works as a cleaner in the offices of a large factory. Two years ago the doctor at the company called all employees in for a medical checkup.

“Your cholesterol is too high,” he told her. “There is a great risk that you will have a heart attack within five years if you don't do anything about it.”

“I felt fit as a fiddle, but he scared me to death,” Karla told me. She doesn’t feel fit any longer.

Karla was sent to the medical clinic at the nearest hospital where the doctor told her to go on a diet. Karla loves to eat and to prepare good food. According to her husband, Karla’s homemade sausages and cheese-cake are famous in their village.

But now they eat mostly vegetable oil and high-fiber foods. When they buy a steak for a special occasion, they cut off all the fat.

“And that’s the tasty part,” Karla sighed. “If only the diet had lowered my cholesterol, but it didn’t.”

“Diet is not enough,” the doctor said. “You also need pills.”

Karla hated the diet, but it was nothing compared to the drug.

“You have to stand a little discomfort,” the doctor told her.

The diet made it easy to slim down, and what was left of her appetite disappeared completely when she started the nauseating medication.

Add to this the demise of her positive attitude. She had looked forward to retirement with her husband, but now all seemed bleak. She felt she had nothing to look forward to.

Her cholesterol went down but not enough, the doctor said, and the dietician looked at her with great skepticism when Karla told her what she ate.

“It’s impossible. You must have eaten more fat than that,” the dietician scolded.

In fact, Karla had eaten some cheesecake the day before, but it hadn’t been a pleasure; she felt terribly guilty afterwards.

Do you think that Karla is unique? Let me tell you about the result of a health project in Luleå, Sweden, headed by Birger Grahn, one of the general practitioners in the district. The aim of the study was to lower the incidence of coronary heart disease. Participants were sent a computerized letter containing a description of their “health profile.” Afterwards Birgitta Olsson, a social scientist, questioned one hundred of the recipients.

Twenty-six of these healthy individuals said the letter frightened them. “It was like a shock,” or “as if the world collapsed,” some of them answered. One stated that she was “almost paralyzed.”

Those with high cholesterol were the most frightened. “The risk that you will have a coronary in five years is estimated to be considerably higher than the average risk for inhabitants of Luleå of the same age and sex as you,” the letter said.

When Birgitta Olsson asked again half a year later, after all the health-promoting activities had started, a further thirteen suffered from anxiety.[1]

You may think that anxiety about cholesterol is something peculiar to the Swedes, but that is not the case. According to a recent Gallup poll in the United States, 56 percent of all Americans worry about fat and cholesterol, 45 percent think that the food they like is not good for them, and 36 percent have guilt feelings when they eat the food they like.

Apart from the fact that worrying about your health may provoke heart trouble, all this stress and anxiety are unnecessary. Karla and millions of others around the world with high blood cholesterol do not know that the cholesterol campaign is medical quackery of the first order. In fact, the eminent American physician and scientist George Mann called the diet-heart idea “the greatest scientific deception of this century, perhaps of any century.”

Unfortunately, Karla and millions of others do not know that high blood cholesterol is nothing to worry about.

This book has been written to give you and your doctor some facts about cholesterol and coronary heart disease. They are facts that even your doctor may not know because these facts have been misunderstood; or because many scientists, health authorities and representatives of the drug companies have suppressed them altogether.

To begin, let me tell you a little about how scientists work.

The scientific method

To bring a little order into a chaotic and hostile world, we try to find the laws that govern the “mess” that we observe. Medical researchers want to

discover the threats against human life and health, and to know what causes disease and premature death, in order to cure or prevent these problems. To this end, we have developed a laborious but highly successful technique called the scientific method.

When we use the scientific method, the first step is to record all the facts about a disease. Who are the victims—men or women, young or old? How do they live and what do they do for a living? What do they eat and drink? What is the chemical makeup of their blood? How clean or dirty is the air they breathe? Scientists meticulously weigh, measure and analyze anything that may be of importance.

Every new piece of the puzzle leads us to speculate about the causes of the disease and to formulate a hypothesis—a theory that we must prove. To see if our hypothesis is correct, we test it in all possible ways. Is some factor present in all cases of the disease? Can the disease be produced by this factor, and can we prevent or cure the disease if we eliminate the factor?

If it doesn't pass all the tests, then our hypothesis is wrong and must be rejected. Then we construct a new hypothesis that we hope will conform better to reality. We test and observe again. If necessary—and it often is necessary—we reformulate our hypothesis and repeat our tests a third and fourth and fifth time until, at last, we have a little nugget of pure truth in our hands. True scientists put the solution to a medical problem first and not the preservation of their own hypothesis, no matter how clever the hypothesis may seem or how proud of themselves they may be for creating it.

Scientists know that it is very rare for their first inspired thought to solve a scientific problem. Therefore, in our search for solutions, we scientists are as much interested in test results that destroy our hypothesis as we are in results that confirm it. And we do not blame anybody for a bad idea, providing that it is abandoned as soon as its flaws become obvious.

Defining our terms

This book is about the idea—the false idea—that a high level of cholesterol in the blood is the main cause of atherosclerosis and coronary heart disease. But what is atherosclerosis? And what is coronary heart disease?

When we grow old our arteries become stiff. The smooth muscle cells and the elastic fibers that surround our blood vessels when we are young are gradually replaced by more or less fibrous and rigid tissue. At the same time, or later on, cholesterol, various fats and even calcium become embedded in the blood vessel wall.

Arteries probably become stiff as a protective measure, to prevent the pressure of the blood inside them from causing them to widen too much. Thus, the remodeling of the arteries does not occur evenly. It is most pronounced where the strain to the artery wall is highest, for instance, where the blood vessels branch. Such localized thickening is called an atheroma or plaque. Atherosclerosis increases with age, as does the blood pressure, and atherosclerosis is most pronounced in individuals with high blood pressure.

The fact that arteries that are prevented from widening, such as those that pass through the bony channels in the skull and the few branches that pass through the heart muscle (most branches lie on the surface of the heart), never become sclerotic also suggests that stiffening of the arteries may be a protective measure. Furthermore, veins never become sclerotic, probably because the blood pressure in veins is very low. If a surgeon replaces a clogged artery with a section of vein, however, this vein, now exposed to the high arterial blood pressure, soon becomes sclerotic.

For unknown reasons, in some people the embedding of cholesterol in the arterial wall becomes irregular and protrudes into the interior of the artery. Sometimes these localized protrusions, called raised lesions, even change into a material similar to limestone. The embedding of cholesterol and lime may also progress until the vessel becomes so narrow that the heart gets too little blood and thus too little oxygen. These constrictions were considered to be the cause of heart attacks, either directly, or by starting the formation of a clot.

When the blood flow to the heart becomes insufficient, symptoms of discomfort radiating from the chest may result, especially if the heart's need for oxygen is increased during exercise. These symptoms are called angina; they disappear if you stop exercising. But if the blood flow is totally arrested, or if it is reduced too much for too a long time, the part of the heart that is supplied by the obstructed branch of the artery will die. This is called

a heart attack, or a coronary, or, more precisely, a myocardial infarction. Angina and myocardial infarction taken together is what we call coronary heart disease, often shortened to CHD.

Atherosclerosis is said to be the cause of coronary heart disease, but the matter is not that simple. Anything that obstructs the coronary arteries may produce coronary heart disease. Studies of the hearts of people who have died from a heart attack have revealed that in about a fifth of the patients there is no evidence of coronary atherosclerosis. The arrested blood flow in such cases may have been due to a spasm of the artery, or to a clot that dissolved before death, but we don't know for sure.

To further complicate the story, a coronary artery may be totally obstructed without any symptoms and without any damage to the heart. The explanation is that the fine branches of the three coronary arteries communicate with each other. If blockage of an artery develops slowly enough, the communicating branches gradually widen, allowing the neighbor to carry more of the blood supply.

Thus, a myocardial infarction may occur even though the coronary arteries are totally normal, and coronary heart disease may be absent even though the coronary arteries may be completely blocked. Obviously, atherosclerosis and coronary heart disease are separate conditions, but many researchers have confused our thinking by considering them as one.

The Diet-Heart idea

In the search for the causes of atherosclerosis and heart disease, researchers since the early 1950s have focused on a single hypothesis or idea. This is the diet-heart idea, sometimes called the lipid hypothesis. As I will explain in this book, the diet-heart idea is a hypothesis that has not passed the basic scientific tests, a hypothesis that is filled with obvious absurdities.

The diet-heart idea is not scientifically sound, but it survives. In fact, the diet-heart idea is hopelessly incorrect, but it seems to have eternal life. It lives on because the researchers who created it and defend it—I will call them the proponents—have not followed the principles dictated by the scientific method.

Those principles demand open-mindedness and objectivity, but the proponents of the diet-heart hypothesis routinely belittle, deny or explain away any scientific observations that contradict their idea. They take the weakest association that supports their idea and call it strong evidence, and they refuse to consider any conflicting observation. In the process, logic becomes as remote as a town in Siberia. Proponents of the diet-heart idea often ask, “What is wrong?” but when they ask this, they mean what is wrong with the conflicting evidence and not with their pet hypothesis. Masses of valid scientific evidence should have destroyed the diet-heart idea by now. Yet, like the ancient Greek Hydra, a mythological monster that grew new heads whenever its old ones were chopped off, the cholesterol Hydra continues its life as if nothing had happened.

But before we look at evidence that should destroy the diet-heart idea, let’s first consider what that idea is.

According to diet-heart proponents, coronary heart disease is the third and final step of a three-step process. In the first step, or so the proponents claim, the amount and the type of fat in our diet determines the level of cholesterol in our blood. They say that if we eat an atherogenic diet, our blood cholesterol will be high. And by an atherogenic diet they mean a diet containing too much cholesterol and saturated fat (found mainly in animal products, such as meat, milk, eggs but also in palm oil and coconut oil) and too little polyunsaturated fat (found mainly in marine animals and commercial vegetable oils). According to the proponents, step two occurs because high blood cholesterol is the main cause of atherosclerosis. And in step three, or so the proponents claim, atherosclerosis causes coronary heart disease by blocking the blood vessels of the heart. The idea sounds simple, and most of us are familiar with it after reading about low-fat recipes and low-fat diets for years in popular magazines and newspapers.

At first glance, the diet-heart hypothesis does indeed appear simple, logical and well founded. It is also an attractive idea, because it almost promises that death from coronary heart disease can be prevented. If animal fat and high blood cholesterol are the villains, then cholesterol-lowering diets and cholesterol-lowering medicines appear to be wise choices. It’s easy to understand why doctors, politicians, pharmaceutical companies and the

manufacturers of vegetable oils and low-fat frozen dinners have embraced the diet-heart idea.

But very few people know that it is built on nothing more than circumstantial evidence. Nobody has ever seen the villains in action. There are many diseases that we have explained from circumstantial evidence but only when all the evidence has pointed in the same direction. As for the diet-heart hypothesis, the evidence is contradictory and confusing. In fact, huge numbers of published medical studies reveal results that are totally at odds with this idea.

For many years, millions of people have endured a tasteless, tedious diet or have suffered serious side effects from cholesterol-lowering drugs because of the diet-heart idea. And billions of dollars have been spent in vain because previous research, reviewed in the chapters to come, had already demonstrated the diet-heart hypothesis to be completely worthless.

Medical experts and health authorities will criticize this book and its author because their prestige is at stake. They will probably describe the author as unscientific or incompetent, and they will say that prestigious committees all over the world have decided that the diet-heart idea has been proved beyond all reasonable doubt.

This book is written for people who can think for themselves. And if you find that something I have written seems too incredible, please consult the references. Then go to a university library and read the original papers yourself. By doing this systematically, as I have done, you will not only see that I am correct, but you will also learn more about cholesterol and the heart than most researchers have. Judging from their papers, many of those researchers seem to have read only reviews, and reviews written by the proponents are notoriously unreliable. In the chapters to follow, I shall give you many examples of misquotations from such reviews.

One of my objections to the diet-heart idea is that its proponents are selective about their data. They lean on studies that support their idea—or that they claim, not always truthfully, support it—and ignore those that contradict them.

One of the proponents once accused me of pointing only to studies that do not support the diet-heart idea and, thus, of using a technique similar to the

one the proponents use.

He was right.

What he failed to remember is that, if a scientific hypothesis is sound, it must agree with all observations. A hypothesis is not like a sports event, where the team with the greatest number of points wins the game. Even one observation that does not support a hypothesis is enough to disprove it. The proponents of a scientific idea have the burden of proof on their shoulders. The opponent does not have to present an alternative idea; his task is only to find the weakness in the hypothesis. If there is only one proof against it, one proof that cannot be denied and that is based on reliable scientific observations, the hypothesis must be rejected. And the diet-heart idea is filled with features that have repeatedly been proven false.

The history of science is one in which many attractive ideas have been discarded when found to conflict with observed fact. For instance, the earth was considered to be a flat planet around which the sun and the other planets revolved. Anyone could ascertain this by looking at the horizontal skyline. And, with his own eyes, anyone could see how the sun, like the moon, circled around the earth.

Our ancestors did not know better because they had only the naked eye and lacked the technology needed to discover the truth. But the proponents of the diet-heart idea ought to know. Instead, their cocksure writings demonstrate that for them the idea has become a fact, the cholesterol earth is flat.

Or is it only a game? Those of you who read this book will realize that scientists who support the diet-heart idea and who are honest must be ignorant, either because they have failed to understand what they have read or else, by blindly following the authorities, they have failed to check the accuracy of the studies written by those authorities. But some scientists must surely have realized that the diet-heart idea is impossible and yet, for various reasons, have chosen to keep the idea alive.

In both politics and religion, ideas can be more powerful than any army. In medicine, ideas can also have powerful consequences.

Let us now explore a medical hypothesis, the diet-heart idea, which, although it seriously conflicts with the laws of logic, has dominated scientific thinking for many years—with many unfortunate consequences.

Myth 1: High-Fat Foods Cause Heart Disease

Some circumstantial evidence is very strong, as when you find a trout in the milk.

Henry David Thoreau (1817-1862)

A challenge

In 1953 Ancel Keys, director of the Laboratory of Physiological Hygiene at the University of Minnesota published a paper, which, looking back seems to have been an early kick-off for the cholesterol campaign.[\[2\]](#)

The horizon for the US Public Health Service is too limited, he wrote; any major disease should be prevented, not only those of infectious or occupational origin.

It doesn't matter that the necessary measures are not yet known. The mere hope that the incidence of a disease may be altered is sufficient reason to invest money and manpower.

What Dr. Keys had in mind was coronary heart disease. This disease is a threat, he continued. While all other diseases are decreasing in the United States, there has been a steady upward trend in the death rate from coronary heart disease. On this particular point the Americans are inferior to other countries; in the US, for instance, four to five times more die from a heart attack than in Italy.

Dr. Keys's reservations regarding the preventive measures were mere rhetoric; he already knew what to do. He considered a defeatist attitude about coronary heart disease despicable. According to Dr. Keys it was "abundantly clear" that heart attacks could be prevented. And he knew the preventive measures. What was possible for the Italians should be possible for Americans also, he added, "These figures are a challenge."

Remember that Dr. Keys was directing these words to Americans, a proud people for whom the word aggressive is a word of honor, in health care as in other matters. In the US more diagnostic tests are made than in any other country; surgery is preferred over drugs, and when drugs are chosen high doses and strong preparations are used.[\[2\]](#) Ancel Keys's words did not go unheeded either.

According to Dr. Keys, fat food was the culprit. His proof was a diagram, which showed that the intake of fat food and the death rates from coronary heart disease followed each other closely in six countries (fig. 1A). The points of the diagram lay as on a string, so that the curve he had drawn looked more like the result of a physical experiment than a biologic relationship. If you prolong the curve at the left it intersects the origin (= the intersection of the axes), thus suggesting that if you avoid fat food completely you will never have a coronary. Wrote a commentator in *The Lancet* the

following year, “The curve shows an almost convincing relationship between the fat content of the food and the risk of dying from coronary heart disease.”

But why did Dr. Keys use the figures from six countries only? At that time information was available from 22 countries and if all of them were included the association was in fact rather weak. For instance, the death rate from coronary heart disease in some countries was 3-4 times higher than in countries where the consumption of fat was the same (fig. 1B).

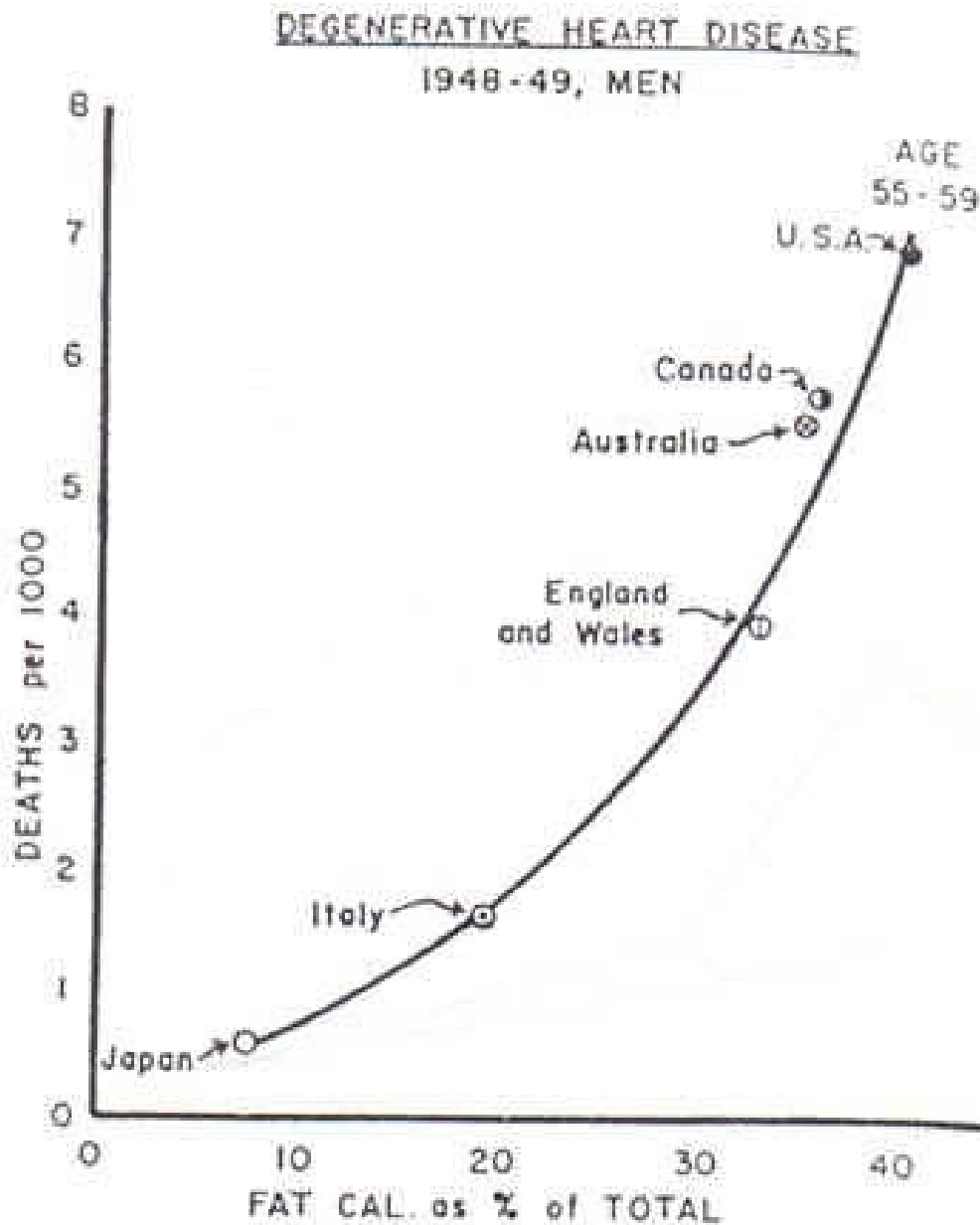
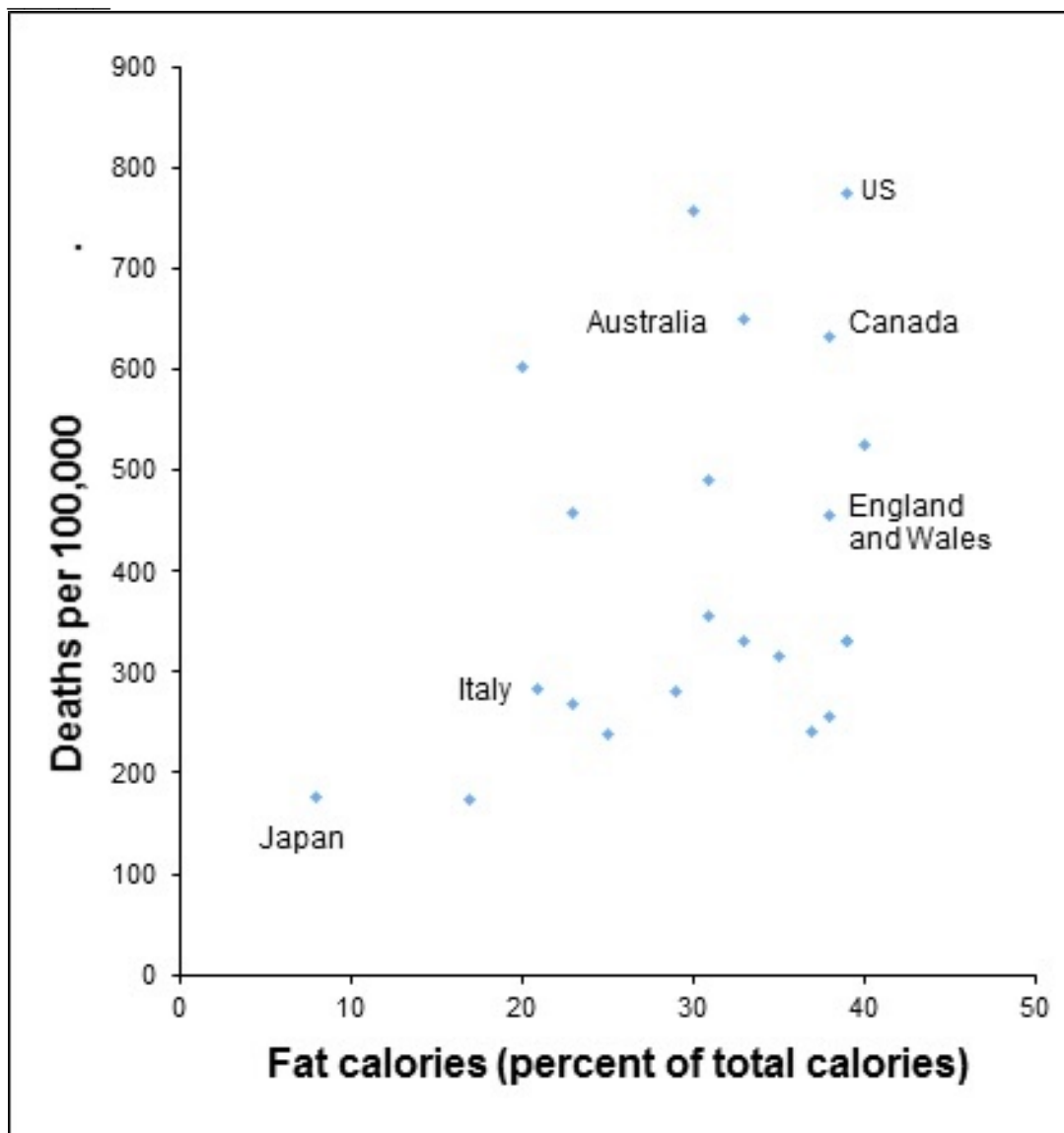


Fig. 1A. Correlation between the consumption of animal fat in percent of the total calorie consumption, and mortality from coronary heart disease in six countries. Data from Keys.[2]

Fig. 1B. Same as fig. 1A, but including all countries where data were available when Dr. Keys published his paper Data from Yerushalmy and Hilleboe.[3]



Are consumption data accurate?

Let us have another look at the figures 1A and 1B because we need to understand the data there. Similar figures are presented again and again by upholders of the diet-heart idea. What do the figures really mean?

Firstly, “Calories from fat” does not mean the amount of fat eaten in each country, only the amount available for consumption. By that is meant the sum of what is produced in the country and what is imported minus food used for purposes other than human nutrition. From this figure, which is the one used in figures 1A and 1B, should be subtracted the amount of fat that is never delivered to the consumers because it is lost, stolen, eaten by rats or mice, or disturbed because of bad storage. Further, some of it is eaten by dogs, cats and other pet animals; and some is thrown away in the kitchen or

left on the plate. In the US where eating fat is considered almost as a sin much fat certainly disappears that way. In poor countries, however, where famine is a greater threat than overweight or heart disease, it is not so. Here, the diet includes even brain and bone marrow, both of which are crammed with animal fat and cholesterol.

Thus, the figures for fat consumption in various countries are most unreliable, to put it mildly. But the figures for heart mortality, those on the vertical axis are even more erroneous.

Are death certificates true?

When statisticians write their reports about numbers and causes of death in a population they consult the death certificates. Do you think that what is written on this piece of paper is the truth and nothing but the truth?

Certainly not. Again and again great differences have been found between the diagnosis set by the doctor while the patient was alive and the findings at the post-mortem. Even doctors with access to modern diagnostic equipment name the wrong diagnosis on the death certificate in one out of three cases.[4] For instance, most doctors consider sudden, unexpected death to be caused by a heart attack due to coronary heart disease. Dr. George Lundberg from University of California and Professor Gerhard Voigt from University of Lund, Sweden showed this to be wrong. In 51 of one hundred such cases, the cause of death was due to something else.[5]

The situation is no better when patients actually have died of heart attacks. Drs. Edwin Zarling, Harold Sexton and Pervis Milnor from Memphis, Tennessee, found that among one hundred patients who died from a heart attack according to the postmortem only fifty-three had a correct diagnosis before they died.[6]

Consider that these studies were not performed in small local hospitals but at university hospitals with access to the finest diagnostic tools of modern medical science in the hands of experienced academic doctors.

Maybe you think that it is unimportant what the doctor diagnoses as cause of death because mistakes will be corrected by the coroner. But postmortems are performed only in a minority of cases; in the US in one out of five, in other countries much less often.

So, if the diagnostic accuracy is that bad in a modern, Western hospital, how do you think it is in poor countries where the cause of death is rarely written by doctors, much less by a coroner?

But even frequent postmortems are no guarantee of a correct diagnosis. This was amply demonstrated by the British professors D. D. Reid and Geoffrey Rose.[7] They collected summaries from the hospital records of ten patients who had died from various heart, kidney and lung diseases. Except for the diagnoses, the summaries contained all information relevant to the cause of their death including results of the

physical and laboratory examinations, statements from the X ray department and the post-mortem descriptions. Then, a number of experienced, academically trained doctors from university hospitals in Norway, England and the US were told: *“Read the records and write the death certificates!”*

Any scientist who considers statistics based on death certificates as a source of truth should look carefully at the fact that coronary heart disease was used as a diagnosis by the American doctors 33 percent more often than by the English doctors, and 50 percent more often than by the Norwegian doctors.

Someone who is not a physician may find it odd that doctors from countries with similar medical traditions and education systems act so differently when they put a diagnosis on the death certificate. The explanation is that there may be serious changes in many organs in a dying person, but on the death certificate and in the statistical tables there is room for only one diagnosis. Thus, in complicated cases American doctors, by unknown reason, are inclined to blame the death on changes of the vessels to the heart, whereas English and Norwegian doctors may instead hold lung or brain diseases responsible. Interestingly, the official death statistics from these three countries show the same tendency.[\[8\]](#)

If death is labeled so differently in the US, England and Norway, where the medical education is similar, how is it labeled in countries such as Japan, Ceylon (Sri Lanka) or Mexico where the culture and medical traditions are fundamentally dissimilar?

Clearly, official death statistics are based on diagnoses which in at least half of the cases are plain wrong, and if they are not wrong, they do not tell the whole truth.

Television—a risk factor?

But let us assume that heart attacks are more common in countries where people eat much animal fat. What does it mean?

From Table 1 you can see that other factors than eating animal fat are associated with heart disease.

Table 1. Correlation coefficients between various consumption factors and mortality in coronary heart disease for men age 55-64 in 22 countries.

| Factor | Correlation Coefficient |
|--|-------------------------|
| Number of cigarettes sold per inhabitant | 0.64 |
| Number of cars sold per 100 inhabitants | 0.58 |
| Total consumption of protein* | 0.72 |
| Consumption of animal protein* | 0.73 |
| | |

| | |
|-----------------------------------|------|
| Total consumption of fat* | 0.56 |
| Consumption of animal fat* | 0.65 |
| Consumption of cholesterol | 0.69 |
| Consumption of sugar* | 0.68 |
| *amount available for consumption | |

The correlation coefficient in the right-hand column of the table tells how well various factors follow the number of deaths from heart attacks in the countries that were studied. The largest coefficient is 1, the weakest is zero. The table thus tells us that in countries where heart attacks are common (meaning where the diagnosis coronary heart disease is commonly used) people eat more protein, fat, cholesterol and sugar. They also smoke more cigarettes and buy more cars than in countries where heart attacks are less common.

What the statistics actually tell you is that the risk of having the diagnosis coronary heart disease written on one's death certificate is greater for people in prosperous countries than for people in poor countries. Therefore, anything that follows with or from prosperity is automatically associated with mortality from coronary heart disease. Calories from animal fat, for instance, are more expensive than calories from other nutrients; people in prosperous countries therefore eat more animal fat than people in poor countries. And since the cause of death more often is called coronary heart disease in prosperous countries than in poor ones, intake of animal fat becomes statistically associated with the number of deaths from coronary heart disease.

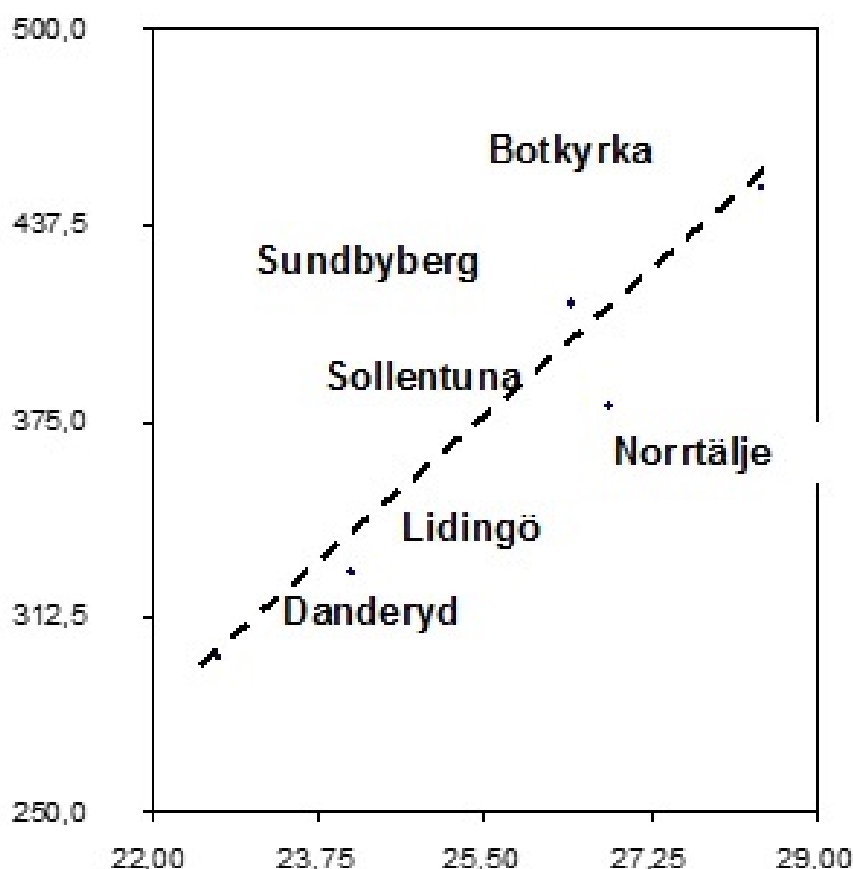
Thus, population studies may point to factors that are associated with a certain diagnosis on the death certificates but they cannot tell us the cause of the disease; only experiments can. Factors which are statistically associated with a disease are called risk factors. A risk factor may be the cause of the disease, but most often it is not. Several hundred risk factors are known for coronary heart disease, for instance smoking, overweight, high blood pressure, lack of exercise, psychological stress, baldness, snoring, and eating too much or too little of a steadily increasing number of various food items, but the cause of the disease is still unknown. What the table demonstrates are just a few examples of risk factors for coronary heart disease.

Because a risk factor and the cause of a disease may stem from a common factor, for instance a country's prosperity, it is self-evident that the elimination of the risk factor does not automatically prevent the disease; the main cause is still there.

Let us assume that the real cause of coronary heart disease is car exhaust. (This is most likely totally wrong but that doesn't matter; I have made this assumption only to demonstrate how factors that vary together may create false associations.) More people are exposed to car exhaust in prosperous countries because cars are more common in

prosperous countries, and as we assumed that coronary heart disease was due to car exhaust, heart attacks should also be more common. Logically, death rates from coronary disease in various countries become associated with the number of cars sold. But people in prosperous countries buy many other things more often, for instance television sets, and thus the coronary death rates also become associated with the number of television sets sold. You may therefore call “possession of a television set” a risk factor although it was not the television set but the car exhaust which caused coronary heart disease. Clearly, it is a bad idea to throw the television set out the window to save the heart.

To carry our example one step further, see figure 1C, which shows the correlation between the tax rate and death from heart disease in the municipal tax districts of the county of Stockholm, Sweden. The graph implies that if the municipal tax rate is lowered to 9.95 percent, no one will die from a heart attack—a challenge to all



politicians!

Figure 1C. Correlation between tax rate and heart mortality in the municipal tax districts of the county of Stockholm.

Vertical axis: Heart mortality per 100,000; Horizontal axis: Municipal tax rate 1976; percentage

Another example. People with yellow fingers die more often than others from a heart attack. “Yellow fingers” is therefore a risk factor for coronary heart disease. But it doesn’t help to scrub away the yellow color, because the discoloration is due to cigarette smoking. The cause of coronary heart disease is not the yellow color, but either the smoke from the tobacco or the paper, or the mental stress that starts the habit of smoking, or a factor associated with the habit of smoking or the feeling generated by nicotine.

Risk factors do not necessarily produce disease. But most diet-heart supporters rarely distinguish between risk factor and cause. They consider every new risk factor as something that should be reduced or eliminated.

Seven random countries

To prove his idea Dr. Keys organized a study of coronary heart disease in seven countries. To this end he selected sixteen local populations in the Netherlands, Yugoslavia, Finland, Japan, Greece, Italy and the US. Men between the age of 40 and 59 were studied. In cooperation with local doctors, scientists and health authorities anything which might conceivably cause coronary heart disease was investigated. The men were followed for about five years, and all heart symptoms and all deaths were recorded.[\[9\]](#)

In each country two or three groups of people were studied. Among other things the investigators looked at the diet, they measured the blood pressure and weighed all participants, and asked how much they smoked and exercised.

The conclusion from this gigantic project was that what best could predict the number of heart attacks in a country was how much animal fat people ate in that country. In countries where people ate much animal fat, heart attacks were common; in countries where people ate little such fat, heart attacks were rare.

But within the countries the number of heart attacks did not follow the diet. Here I shall tell about the two Finnish populations; the one from East Karelia and that from Turku; in another chapter I shall tell about the people on two Greek Islands.

At the start, forty-two of 817 men from East Karelia had coronary heart disease, in the district of Turku only fifteen of 860. And during the next five years sixteen men died from a heart attack in Karelen, but only four in the district of Turku. Taking all factors in consideration heart attacks were seen five times more often in Karelen than in the district of Turku.

If you think that the natives lived especially carelessly in Karelen you are wrong. The living conditions in the two areas were practically identical. These people lived isolated as farmers or lumberjacks, their body weight and height were identical, they smoked equally much, and they ate the same amount of polyunsaturated fat. The blood pressure was a few percent higher in Karelen, and here they also ate a few percent more animal fat than around Turku.

Dr. Keys declared that coronary heart disease was five times more common in Finland than in Japan because of the food, but he did not explain why coronary heart disease was five times more common in eastern than in western Finland although the difference between the common risk factors was only marginal. He mentioned it as a minor, abnormal finding which he (erroneously) stated would be explained by further studies.

This way of arguing is common among the proponents to the diet-heart idea. Observations that support this idea are trumpeted forth as positive proofs while unsupportive findings, if they are mentioned at all, are considered as “rare exceptions” or “something which cannot yet be explained.”

Up and down in statistics

To see if fat food causes heart attacks it should be of interest to study how the eating habits in a country have changed during a period of time and to ask if the number of heart attacks has changed in the same direction. If animal fat is an important cause of coronary heart disease the number of heart attacks should increase during periods of increasing intake of such fat; and it should decrease when less animal fat is eaten.

But even if these figures follow each other up and down, we have not proved that eating animal fat is the cause of the increasing mortality. Again an unknown factor could create parallel changes in fat intake and heart mortality. Let me give an example.

During World War II people in Finland, Norway, Sweden and Great Britain died less often from heart attacks than before the war. Said Haquin Malmroos, a professor of medicine in Lund, Sweden: *“this is because people ate less animal fat.”*

But other things of importance for heart disease occurred during the war. For instance, people's body weight and blood pressure went down considerably, fewer people smoked, and the lack of gasoline for cars and other machinery should also have favored a healthier way of life. A common denominator of the war was lack of goods—lack of fat food for instance, but also lack of other nutrients and of gasoline and cigarettes. Nobody knows which of these factors, if any, caused the decrease in heart disease. The explanation that people ate less animal fat is unlikely because it has never been possible to lower the death rate from coronary heart disease with a low-fat diet in experiments of the same length as World War II. Furthermore, the mortality curves turned upwards again long before the increase of the consumption of animal fat took place.

Thus, although a risk factor changes parallel to the death rate it is not necessarily the cause. But if the risk factor is the cause, its rise and fall must be reflected in the death rate from the disease. If heart attacks are caused by eating too much animal fat, heart attacks should of course become more frequent if people started to eat more of such fat. Likewise, if people changed their diet and ate less animal fat, fewer heart attacks should occur. This is not so.

From World War I up to the 1980s, the number of deaths from heart attacks increased substantially in most countries while the intake of animal fat decreased or was unchanged. For instance, the death rate from cardiovascular diseases of middle aged Yugoslavians increased three to four times between 1955 and 1965, while the intake of fat decreased by 25 percent.[\[10\]](#)

In England the intake of animal fat has been relatively stable since at least 1910 while the number of heart attacks increased ten times between 1930 and 1970.

In the US coronary mortality increased about ten times between 1930 and 1960, leveled off during the 1960s and has since decreased slowly. During the decline of heart mortality the consumption of animal fat declined also, but during the thirty years of sharply rising coronary mortality the consumption of animal fat decreased.

In Framingham the number of fatal heart attacks went down during the decline of animal fat consumption, but the number of non-fatal heart attacks increased with the same number. The authors of the Framingham report explained this discrepancy by saying that it takes much longer time to lower the number of non-fatal heart attacks than to lower the number of fatal cases.[\[11\]](#) (A much better explanation is, that to-day more people survive a coronary because of improved treatment).

In Japan the number of fatal heart attacks between 1950 and 1970 increased as did the intake of animal fat appearing to confirm the diet-heart idea. But the increase in coronary mortality was seen only above the age of 70 and especially above 80. In the latter age group, the increase in coronary mortality more than counterbalanced the decrease in the other age groups. In other words, younger Japanese people died less often of coronary disease, although they ate more animal fat. During the same period mortality from most diseases decreased in Japan. Thus, the increasing death rate from coronary disease among old people in Japan could not be caused by an increased intake of animal fat; if it were, the number of coronary deaths should have increased in all age groups. The explanation is that the general health in Japan has improved steadily since the war, as has the people's mean length of life. Many more have become old, and since coronary heart disease is a disease of old age, the death rate due to heart disease has of course increased.[\[12\]](#)

This torpedo against the diet-heart idea was presented as the first paper at an international conference in 1981. Yet the paper created no intellectual explosions. The author of the paper, Dr. Kimura concluded: "... *if this food supply and nutrient intake*

pattern continues the same evolution in Japan, incidence of ischemic heart disease will increase in the future."

And the conference continued with paper after paper acknowledging the diet-heart idea. But in spite of a continuing increase in the intake of animal fat in Japan also after 1970, and a steady increase of the mean serum cholesterol level the number of fatal heart attacks decreased in all age groups, contrary to Dr. Kimuras prophecy.

While the death rate from coronary disease increased in most countries after World War II it decreased in Switzerland. If this decrease had been followed by a decline in the intake of animal fat, Switzerland would have been a model for health care in other countries. But Switzerland is never mentioned because parallel with the declining heart mortality, the Swiss intake of animal fat increased by twenty percent.[\[13\]](#)

The shepherds of Kenya

The many exceptions to Ancel Keys's hypothesis indicate that something in the Western life style other than fat food is the cause of coronary heart disease. To be absolutely sure it is necessary to study people who eat just as much animal fat as we do but who are not exposed to the menaces of Western civilization. If the diet were the most important factor people in such countries would have equally high cholesterol and die just as often from heart attacks as we do.

In the early 1960s, Professor George Mann and his team from the Vanderbilt University in Nashville, went to Kenya in Africa with a mobile laboratory to study the Masai people.[\[14\]](#) The diet-heart idea had just started its triumphal progress. Professor Mann had heard that the Masai people did not eat anything but milk, blood and meat. Wouldn't it be a good idea to test the diet-heart idea on the Kenyan plateau? Shortly before and with the same purpose Dr. Gerald Shaper from the Makerere University of Uganda had traveled a little further north to another tribe, the Samburus.[\[15\]](#)

The Samburus and the Masai people are slender people who have survived as shepherds for thousands of years. Their life is free from the mental stress and competition of Western civilization, but you cannot call it comfortable. Every day they walk or run many miles with their cattle, searching for food and water.

Their own diet is extreme. According to their view, vegetables and fibers are food for cows; they themselves eat milk, meat and blood only, or at least the younger men do. A male Samburu may drink almost a gallon of milk each day. He has never heard about the cholesterol campaign, and therefore he drinks the creamy milk as it is, which means that his intake of animal fat is far above that of most Western people. Also, his intake of cholesterol is high, especially during periods when he adds 2-4 pounds of meat to his daily diet.

Masai people drink “only” half a gallon of milk each day. However, they eat more meat than the Samburus. Their parties are sheer orgies of meat; on such occasions 4-10 pounds of meat per person is not unusual, according to Professor Mann.

If the diet-heart idea was correct, coronary heart disease should be epidemic in Kenya. But Mann found that no Masai dies from a coronary. Rather, the Masai people would die of laughter if they heard about the cholesterol campaign.

But this was not the only surprise. The cholesterol of the Masai tribesmen was not sky-high as Mann had expected; it was very low. In fact, their cholesterol was among the lowest ever measured in healthy people, about fifty percent of the value of most Americans.

Another cholesterol safari

Now to Dr. Bruce Taylor from Chicago. He was the first to induce a coronary in an ape by cholesterol feeding (see Chapter 6). The papers about the Samburu and the Masai people were published shortly after Dr. Taylor’s successful experiment. Certainly he must have asked himself why the cholesterol of his laboratory animals skyrocketed on their fat diet, but not the cholesterol of the Masai and the Samburu people. To answer this question he was on his way to Kenya with his own expedition a few years later.

Like other mammals, we produce cholesterol ourselves, day and night. When we eat lots of cholesterol or animal fat, our own production of cholesterol decreases automatically. If we eat only a little, our production increases. This mechanism keeps the cholesterol level in the blood fairly constant and explains why it is so difficult to lower cholesterol with diet. After his investigations Dr. Taylor reached an unusual conclusion about this balancing mechanism in the Masai people.

According to Dr. Taylor the African tribes do not contradict the diet-heart idea because their ability to reduce their own cholesterol production is superior to other people. Because the Masai people have been isolated from other tribes for many thousands of years, they have developed this ability so well that it has been built into their genes, Taylor said. Taylor and his colleagues considered their results so important that they published them with minor variations in four different scientific journals.[\[16\]](#)

In science there are often alternative explanations to a new observation, and most scientists therefore discuss which model or hypothesis the new piece of evidence fits into the best. But Taylor did not. He could have considered the possibility that it is not the Masai people who are superior to others in reducing their cholesterol production but instead, we who are inferior, perhaps because of environmental factors, perhaps because we are less active than the Masai people, or perhaps because of something we haven’t yet imagined. But he did not.

It would have been possible to get an answer to these questions if he had continued his expedition to the city of Nairobi and studied Masai people there to see if some factor associated with the more comfortable life style of a big city might have increased their cholesterol. This method is often used by the defenders of the diet-heart idea to demonstrate that low cholesterol goes up when people from poor, undeveloped countries with a low fat intake move to a more prosperous and technologically developed country where the fat intake is high.[17]

But in this case, the study concerned human beings who already ate more fat than ever recorded. After migration to Nairobi their diet most probably became more diversified, and if the diet-heart idea was true their blood cholesterol should have become even lower.

What had happened with the cholesterol of the urbanized Masai people? Why did Taylor and his colleagues not proceed to Nairobi to get an answer to this simple question?

Taylor's explanation that the low cholesterol of the Masai people is genetic is not a valid one. Acquired properties are not transferred to people's descendants. This idea was abandoned as scientifically wrong many years ago. An inborn metabolic trait—in this case the ability to reduce the body's own production of cholesterol when presented to large amounts of cholesterol in the diet — is either present in the genes, or it arises by mutation. If the property is important for survival, the number of individuals with this property increases over time, and eventually these people may outnumber those without it. But this will happen only if the inborn trait improves survival before sexual maturity. Individuals with a trait that protects them against a disease, which strikes after sexual maturity, such as coronary heart disease, do not outnumber individuals without this trait, because the latter transfer their defective genes to their children before they develop the disease.

And, contrary to Taylor's statements, the Masai people are not an isolated tribe. They are warlike people who have taken cattle and women from the neighboring tribes for thousands of years. In this way they have achieved a steady genetic renewal in their cattle and in themselves.

But what finally proved that Taylor was wrong was a study of Masai people living in the big city of Nairobi performed by Dr. José Day at St. Mary's Hospital in London. Again, if the low cholesterol of the Masai was inherited it should have been even lower in Nairobi, because here their diet should most likely include less animal fat than the diet of the Masai tribesmen. But the mean cholesterol level in twenty-six males in Nairobi was twenty-five percent higher than that of their cattle-breeding colleagues in the countryside.[18]

Taylor's genetic explanation has been popular among upholders of the diet-heart idea, such as Dr. Keys. He wrote: "... *the fact is that the peculiarities of those primitive*

nomads have no relevance to diet-cholesterol-coronary heart disease relationships in other populations.”[19]

Taylor studied not only blood cholesterol but also atherosclerosis in the Masai. It was important to show that their low cholesterol level protected the Masai people from atherosclerosis. Ten aortas from deceased Masais were sent to New York where the pathologists said that atherosclerosis was almost absent.

But Professor Mann studied a much greater number of hearts and aortas from Masai people of all ages and found that the coronary vessels of Masai people were just as atherosclerotic as those from US citizens, perhaps even more. But severe sclerotic changes, so-called plaques or raised lesions, were rare; the sclerotic changes were situated inside the vessel walls whereas the inner surface of the vessels was smooth. And in the fifty hearts he studied there was no evidence of myocardial infarctions in any.

Professor Mann thought that the Masai were protected from coronary heart disease by the size of their coronary arteries. These were much wider than those of most Western people, probably because the hearts of the Masai have worked hard while the men were running after the cattle. Many of the Masai people Mann examined were splendidly fit, as good as, or better than, superior sportsmen. It is no coincidence that the world's best runners tend to come from Kenya.

Thus, it is possible to gorge on cholesterol and animal fat and still keep the blood cholesterol very low. The diet-heart idea should be smashed after such evidence, and the message about the Masai and Samburu people should challenge any defender of the diet-heart idea. But the idea is still flourishing, and nobody seem challenged. In fact, the Masai and the Samburu people are not mentioned at all in the official reviews of the diet-heart idea.

It is worth mentioning another interesting observation from Kenya. In that country there are many Indian emigrants. Although they all come from India their diet are not similar. Non-Muslim Indians from Gujarat live on a lactovegetarian diet while Muslim Indians from Punjab eat eggs and meat and drink twice the amount of milk as their compatriots from Gujarat, and they never use vegetable oil. The non-Muslim Indians thus live as if they had been listening to the cholesterol campaign to avoid coronary heart disease, while the Muslims act as if they're doing what they can to get it. But the mortality rate from coronary heart disease is equal in both populations.[20]

However, this aberration from the diet-heart idea seems petty compared with the next one. Curiously, Dr. S. L. Malhotra from Bombay, India is never cited in the many reviews advocating for the prudent diet. He studied coronary heart disease among more than one million male employees of the Indian railways. During a five-year period he recorded 679 deaths from that disease. Most cases, 135 per 100.000 employees, were

noted in Madras in southern India; fewest cases, 20 per 100.000 employees, were noted in Punjab in northern India.[\[21\]](#)

Thus, death from coronary heart disease was seen about seven times more frequently in Madras, and those who died were on average twelve years younger than in Punjab. But in Punjab, people ate 10-20 times more fat, and they smoked eight times more cigarettes. And while the small amount of fat that people ate in the weak-hearted province of Madras was mainly of vegetable origin, the fat they gorged on in the strong-hearted Punjab was mainly of animal origin.

Have coronary patients eaten more fat?

A way of searching for the cause of a disease is by using the so-called case-control study. In a case-control study scientists question randomly selected control persons of the same age and sex and from the same geographic area as the patients with the disease under investigation. In which way do the patients differ from the controls? What do they do for a living? How much do they smoke and drink? What do they eat? Are they fatter or slimmer than the controls? How is their blood composed? Are they exposed more than the controls to environmental pollutants? Only your imagination and your money put a limit to your questions.

In North Dakota in the USA, Dr. William Zukel and his team performed a case-control study. They studied all the men who had had heart symptoms during one year; for each case they chose two healthy men of the same age as the controls. Dr. Zukel was especially interested in the diet of the participants during the month before the first symptoms or before the interview. If the interviewee had died, his wife or nearest relatives were questioned.[\[22\]](#)

Altogether 228 men had had symptoms of coronary disease. A detailed description of the diet was gained from 162 of them. The conclusion of the study was that control individuals were more often manual workers, and patients were more often smokers. But the diet did not differ between patients and control individuals; they ate the same amount of saturated and polyunsaturated fat, and their caloric consumption did not differ either.

In Ireland another group of researchers under the guidance of Dr. Aileen Finegan performed a similar investigation. For a whole year they studied the diet of one hundred men who had suffered from a heart attack. Their diet was compared with that of fifty healthy men of the same age.[\[23\]](#)

Dr. Finegan and her team could not find any dietary differences; the patients had eaten practically the same amount and kind of fats as the control individuals.

A similar study was performed in collaboration between researchers from Harvard and the University of Dublin in Ireland under the guidance of Dr. Lawrence Kushi. Irish

men and their brothers who had been living in Boston for at least ten years were selected. These two groups were compared with each other and with a third group of adult sons of Irish emigrants in Boston, a total of one thousand men. Now to the questions. How many would die from a coronary during the next twenty years? And did their way of living differ from that of the others?[24]

The researchers did not get a simple answer. Relatively speaking, more Boston brothers had died from a heart attack than either of the other two groups, but the difference was so small that it could well have been due to chance. It could also have been because the Boston brothers smoked more often and because their blood pressure was higher. The notion that their diet played an important role is unlikely because, contrary to the diet-heart idea, the men in Boston had eaten less animal fat and less cholesterol than the Irish brothers, and more polyunsaturated fat than the emigrants' sons. And there was no difference between the blood cholesterol values of the three groups. Yet, in spite of these negative findings this study is often cited as a strong support of the diet-heart idea.

Another "proof" of the diet-heart idea is a study performed in cooperation between the National Heart, Lung and Blood Institute and the University Hospital in Puerto Rico, conducted by Dr. Tavia Gordon. In Framingham, Puerto Rico and Honolulu more than sixteen thousand healthy, middle-aged men were questioned about their dietary habits. Six years later the dietary habits of those who had had a heart attack were compared with the habits of those who had not.[25]

In Puerto Rico and Honolulu heart attack victims had eaten less starch than the others; in Framingham they had eaten smaller amounts of other carbohydrates. Eating starch or other carbohydrates should therefore protect against coronary heart disease according to the authors of the report.

But the percentage of calories from starch did not differ between the healthy individuals and the patients except in Framingham, where those who had suffered a heart attack had eaten more starch than the others.

In Puerto Rico and in Honolulu those who had had a heart attack had eaten more polyunsaturated fat than those who had not had an attack. Although this observation is contrary to what was expected and thus most discouraging for those who advise people to eat more of such fat it was not mentioned in the summary of the paper.

A similar study was performed by researchers from Framingham and Honolulu, led by Dr. Daniel McGee of the Framingham Heart Study. They asked 8000 Japanese migrants in Hawaii about their diet over a 24-hour period, and ten years later they compared the diet of those who had suffered a heart attack during the ten years with the diet of those who had not.[26]

Those who had suffered a heart attack had eaten just as much animal fat and protein but less carbohydrates as the others. The authors therefore recommended either eating more carbohydrates or less animal fat; either way should have the same preventive effect. In the summary of the report from the study, the authors did not mention that the difference between the diets in the two groups was not greater than what could have been produced by chance.

Today (1998) a total of 27 similar studies have been published including 34 groups (cohorts) of patients and control individuals.[27] Totally, the incredible number of more than 150,000 individuals have been investigated. In three of these 34 cohorts patients with coronary disease had eaten more saturated or animal fat than the control individuals, in one cohort they had eaten less, in the rest no difference was seen. In three cohorts the patients had eaten more vegetable or polyunsaturated fat than the control individuals, in only one they had eaten less.

In the studies mentioned above, the researchers try to press the figures down into the cholesterol shoe, but neither heels nor toes fit in. According to some authorities, we should eat less saturated fat; according to others we should eat more polyunsaturated fat. Still others recommend carbohydrates, if not starch, or fibers, or vegetables, depending on the haphazard results of the most recent investigation.

More critical diet-heart supporters object that information about the diet is unreliable; people simply cannot remember exactly what they have eaten. This objection is correct, of course. The point is, however, that these unsupportive results are used as support, even in the most prestigious reviews. Listen for instance to the words from the review *"Diet and Health,"* published by the *National Research Council: "Percentage of calories from SFAs [saturated fatty acids] was positively associated with risk of CHD in the rural sample of the Puerto Rican and the Ireland-Boston studies."*[28]

If you go to the library and look into the tables of these papers you will see that the differences found were not statistically significant, which means that the results were simply due to chance. And why did the authors of *Diet and Health* only cite these two studies? Why didn't they mention that, if anything, coronary patients have eaten more polyunsaturated fatty acids?

Or listen to the joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute: "... showing the link between diet and CHD particular impressive results [were produced in] the Western-Electric, the Honolulu Heart, the Zutphen, and the Ireland-Boston studies." [29]

Looking into the tables from these reports it appears that only in the Honolulu Heart study the patients had eaten significantly more saturated fat, but in that study they had eaten significantly more polyunsaturated fat also, opposite to what we should expect.

In conclusion, there is a weak association between the coronary mortality in various countries and the amount of fat available for them to eat, but no difference between the amount of fat eaten by coronary patients and by healthy individuals. This is no paradox, but typical of factors that follow each other roughly because they have a common cause. The mean income in various countries, for instance, parallels the number of heart attacks; coronary heart disease is common in rich countries and low in poor countries. But in rich countries poor people die more often from heart attacks than rich people.

Again, calories from animal food are more expensive than calories from vegetable food. The common denominator for countries where people eat lots of animal food is prosperity. In prosperous countries fat food is abundant, but so also are stress-provoking factors. Also more people smoke, fewer people perform manual labor, industrial pollution of the environment is most often worse, and the ability to diagnose coronary heart disease is better. People in prosperous countries also live longer; instead of dying from infectious diseases or malnutrition when they are young they die from diseases related to old age such as coronary heart disease. Any of these factors, or their combination, or something else that I have not thought about, may explain why people die more often from a heart attack in prosperous countries.

Prosperity, fat food, and coronary heart disease thus follow each other. Statistical correlations may therefore arise when different countries are compared, especially if countries that do not follow the usual pattern are excluded. But inside the countries there is no correlation because it is not prosperity or the fat food itself that cause coronary disease.

Triglycerides

Most of the fatty acids in the diet and in the blood are bound to a type of alcohol called glycerol. Usually each glycerol molecule is attached to three fatty acids, and this molecule complex is called a triglyceride. Often shortened to TG. As with cholesterol, high TG levels in the blood have been found to be associated with a higher risk of coronary heart disease. Does that mean that we should lower the level of TG in our blood?

To answer this question satisfactorily demands careful reading and a long explanation. However, if you understand the fallacy of the cholesterol hypothesis, then it will be easy for you to understand that you do not need to bother about your TG either because even the most zealous proponents of pharmaceutical intervention admit that the evidence for high TG causing atherosclerosis and cardiovascular disease, is weak, much weaker than for high cholesterol. Thus, if it is weak or nonexistent for cholesterol, why bother about TG?

The TG level in the blood depends on many factors. Normally TGs go up after a meal. The more fats and carbohydrates you eat—and the more alcohol you drink—the higher your TG level becomes. Almost 12 hours must pass before the level returns to “normal.” An analysis of TG is therefore meaningless if the patient hasn’t been fasting the previous 12 hours.

Furthermore, overweight people have higher levels of TG than thin people, smokers have more than non-smokers, diabetics have more than non-diabetics, people who lead a sedentary lifestyle have more than physically active people, and people under stress have more than people who are on ease. For instance, you could ask whether overweight, smoking, inactive and stressed diabetics with high TG are more at risk than overweight, smoking, inactive and stressed diabetics with normal TG.

In addition, analysis of TG is highly inaccurate and the normal fasting levels are highly variable. If a blood analysis finds 200 mg per deciliter, the true TG level may be anything between 100 and 300. To get a more reliable measure of your normal TG, it is therefore necessary to calculate the

average of three measurements made at three different occasions, each time preceded by a 12-hour fast.

So, when researchers say that high TGs predict an increased risk for heart disease, the question is, whether this is caused by sedentary lifestyle, or smoking, or overweight, or mental stress, or diabetes, or a risk factor we don't know about yet; or whether it is caused by a high TG. And even if a 10-20 percent higher fasting value of TG is associated with an increased risk, it seems senseless to try to lower TG when TG rises after each meal to levels that can be several hundred percent higher than the fasting state. All of us who eat three times a day and drink a glass of wine or whisky now and then simply have "too high" TG most of the time.

Myth 2: High Cholesterol Causes Heart Disease

In our need to understand, to explain, and to treat, the temptation to impute causality to association is pervasive and hard to resist. It is the most important reason for error in medicine.

Petr Skrabanek and James McCormick
Authors of *Follies and Fallacies in Medicine*

Large and small percentages

Framingham is a small town near Boston, Massachusetts. Since the early-1950s a large number of Framingham citizens have taken part in a study surveying all factors that may play a role in the development of atherosclerosis and heart disease. Among other things their cholesterol was measured frequently.[\[30\]](#)

After five years the researchers made an observation, which should become one of the cornerstones in the cholesterol issue. When they classified the citizens into three groups with low, medium and high cholesterol values they saw that in the latter group more had died from heart attacks than in the two other groups. A high cholesterol level predicted a greater risk of a heart attack, they said; high cholesterol is a risk factor for coronary heart disease.

The predictive value of blood cholesterol levels was confirmed in the greatest medical experiment in history, the Multiple Risk Factor Intervention Trial, also called MR.FIT. In that trial researchers measured the blood cholesterol of more than 300.000 American middle-aged men.

Six years later the director of MR.FIT, professor Jeremiah Stamler and his coworkers from Chicago asked how many of these men had died and from what.[\[31\]](#) The participants were then divided into ten groups of equal size, so-called deciles, according to their cholesterol values. The first decile thus consisted of the tenth of the men with the lowest cholesterol, the tenth decile of the tenth with the highest cholesterol.[\[32\]](#)

The researchers analysis showed that in the tenth decile four times more men had died of a heart attack than in the first decile. Professor Stamler's team put it in another way: *"the risk of dying from a heart attack with cholesterol above 265 mg/dl (6.8 mmol/l) was 413 percent greater than with cholesterol below 170."*

With statistics you can change black to white, or vice versa; as any politician will tell you. Four hundred and thirteen percent! A frightening figure.

But let us look at the real figures and not only at the percentages. How many men had, in fact, died from a heart attack?

The total number was 2258, or 0.6 percent of the more than 300,000 men investigated. We could also describe these results by saying that 99.4 percent did *not* die from a heart attack.

Among those with the highest cholesterol value (the tenth decile) 494, or 1.3 percent, died from a heart attack. Said in another way, 98.7 percent of those with the very highest cholesterol values were alive after six years.

Among those with the lowest values, the first decile, ninety-five men, or 0.3 percent, died from a heart attack, while the rest, 99.7 percent survived. Thus, the difference in numbers of death between the first and the tenth decile was only one percentage point (99.7% — 98.7%).

One percentage point doesn't have the same alarming effect as Dr. Stamler's 413 percent, but both figures are correct because 1.3 is 413 percent of 0.3.

The excess of deaths was most pronounced in the tenth decile. It should be remembered that almost all individuals with the rare, inherited abnormality called familial hypercholesterolemia must have been included in the tenth decile. These people have considerably higher cholesterol values than normal individuals and some of them have severe atherosclerosis and cardiovascular disease in early life. A little less than one percent of humanity have familial hypercholesterolemia or some other kind of genetic problem that interfere with cholesterol metabolism. This means that about ten percent of the tenth decile (10 x 1 percent) were abnormal in this respect. Thus, in a complicated way, the statistics demonstrated what we already knew—that patients with an inborn error of cholesterol metabolism have a greater risk of dying from heart disease.

There are more ways that risk factor statistics can be used to magnify trivial differences. Let us go back to the Framingham study.

Great or small differences?

To illustrate the association between blood cholesterol and the risk of dying from a heart attack the researchers from Framingham constructed an interesting graph, shown in **figure 2A**.[\[33\]](#) Two bell-shaped curves are seen. The horizontal axis, or x-axis, represents levels of blood cholesterol while the vertical or y-axis concerns the number of individuals.

The curves in figure 2A are called Gaussian or "bell" curves. When plotted in a diagram like figure 2A, all measurements in biology usually produce a Gaussian curve with a distinctive parabolic or bell shape that rises slowly from the baseline on each side and then rapidly increases in slope at the center. The total area under the curve gives the number of individuals investigated. If, for example, you graph the heights of a random number of people, short individuals will be situated in the area beneath the curve's left slope, and tall individuals will be situated in the area beneath its right slope. When a bell curve is symmetrical, the mean value of the group lies at the top of the curve.

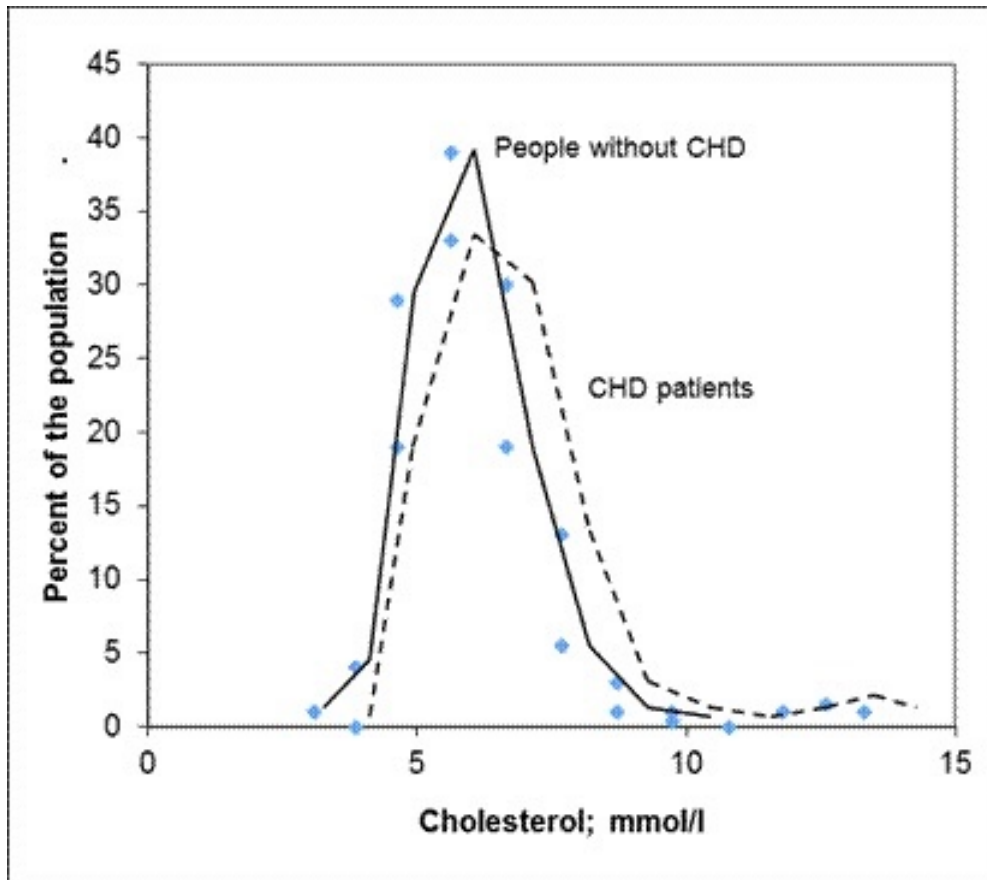


Figure 2A. The distribution of the participants in the Framingham project according to their initial blood cholesterol. The solid line represents 1378 individuals without coronary disease at follow-up; the broken line represents 193 individuals who had coronary disease at follow-up. Data from Kannel and others. [34]

Let's take a careful look at figure 2A. The broken line represents the cholesterol level of all middle-aged men in the Framingham study, who sixteen years after the start of the project had suffered a heart attack. The unbroken line represents the cholesterol levels of the men who had not. The first group consisted of 193 individuals, the other of 1378, but the curves are of an equal size because the vertical y-axis gives percent instead of the number of individuals.

The curve representing the patients is slightly asymmetrical with a little hump far to the right. Otherwise, the two curves appear identical except that the curve of the coronary patients is placed a little to the right; their cholesterol values are approximately 5-10 percent higher than the values of those who remained free of cardiovascular disease.

Most people probably think that those who have a heart attack almost always have large amounts of cholesterol in their blood. The curves demonstrate however that the difference is marginal. In fact, the graph shows that almost half of those who had a heart attack had low cholesterol.

According to the diet-heart idea this small difference in blood cholesterol is one of the most important causes of atherosclerosis and coronary heart disease. But as we shall see, the difference may be due to several other factors.

No risk after forty-seven

Thirty years after the first cholesterol measurement in Framingham the researchers again asked themselves what had happened.^[34] This time, a few more of those with high cholesterol had died. I use the words *few* for a reason. On average one percent of all men with high cholesterol died each year during these 30 years. During the first ten years about a quarter of one percent died each year. As time passed the percentage that died each year naturally grew larger and larger. Among those with the lowest cholesterol values only half as many died; and as in almost all earlier investigations women with low cholesterol died equally often as did women with high cholesterol.

But these figures concerned *all* causes of death. Nothing was said about *heart* mortality! (Why did the researchers from Framingham forget to tell about heart mortality, the main issue of the whole project?)

Now to the most interesting point. For men above forty-seven no difference was seen. Those who had low cholesterol at the age of forty-eight died just as often as those with high cholesterol.

Thus, the Framingham study showed that if you reach age forty-seven, it doesn't matter whether your cholesterol is high or low! I have never met any believer in the diet-heart idea who has even raised an eyebrow when confronted with this astonishing fact.

Blood cholesterol is usually at its highest level at about the age of fifty. It is after this age that heart attacks usually appear, increasing in frequency year by year. After age fifty atherosclerosis also accelerates, but the first signs of atherosclerosis in the artery appear much earlier, between the ages of 20 and 30.

Atherosclerotic lesions are a kind of inflammation involving the smooth muscle cells, the elastic fibers and the white blood cells. In the early stages cholesterol may not be present at all. Much later, usually after age 50, cholesterol and various lipids may be deposited in the lesions, eventually resulting in the dangerous raised lesions.

With these facts in mind how do you explain that high cholesterol is dangerous at the age of 30, but not after 47? If high cholesterol produces atherosclerosis because its level in the blood is a little higher than usual, why is high cholesterol a risk factor at the age of thirty, where cholesterol is rarely found in the arteries, but not after 47, the period of life where most of arterial cholesterol is produced?

Furthermore, few die from a heart attack before the age of 48, and most of them who do die are diabetics or have a rare, genetic problem. More than 95 percent of all heart attacks occur in people older than 48. If cholesterol has importance only for the very few who have a heart attack before 48, why should the rest of us worry about high-fat food and blood cholesterol?

The Framingham findings are not a rare exception. High cholesterol has no importance in old Australians either, according to a study by Dr. L. A. Simons and his coworkers at St. Vincent's hospital in Sydney.[35] Similar findings were uncovered in a study by Dr. Peter Zimetbaum and his coworkers at the Albert Einstein College of Medicine in the Bronx, NY.[36] They found that neither total nor LDL cholesterol predicted the risk of having a heart attack or any other cardiovascular disease in very old men. Curiously, the authors concluded that, "The findings of this study suggest that an unfavorable lipoprotein profile increases the risk for cardiovascular morbidity and mortality."

Unfortunately this happens all too frequently. Researchers get a result that is contrary to the cholesterol hypotheses, and yet they write conclusions indicating that their findings are in support. These misleading conclusions are most often written up in the summary of the papers, the only part of the paper that most doctors and researchers are likely to read. To find the contradictory results, you have to read the whole paper and meticulously study the tables.

In the elderly high cholesterol even seems to be protective. This was the surprising finding of Dr. Harlan Krumholz at the Section of Cardiovascular Medicine at Yale University and his coworkers. They followed 997 elderly men and women living in the Bronx, NY for four years. During a four year period about twice as many of the individuals with low cholesterol had a heart attack or died from one, compared to those with the highest cholesterol levels.[37]

Let me return to the study of the Framingham group. Perhaps you think that the cholesterol campaign was cancelled after the results of the Framingham study came in. Not at all. The reason low cholesterol levels were associated with greater mortality, said the investigators, was that people with low cholesterol levels were dying of other diseases. But their results contradicted that explanation. Wrote the authors: "Those whose cholesterol had *decreased* by itself during these 30 years ran a *greater* risk of dying than those whose cholesterol had *increased*. To cite the report: *For each 1 mg/dl drop of cholesterol there was an 11% increase in coronary and total mortality.*"

Thus, not only total mortality but also coronary mortality had increased.

Now, stop for a moment! For many years we have been told how important it is to lower our cholesterol to prevent coronary heart disease. But the Framingham study demonstrated that if the cholesterol decreases by itself, the risk of dying *increases*.

Few people know about this alarming finding and the study is rarely discussed in the medical reviews of cholesterol and heart disease. Even worse, when the study is noted, it is cited as *supporting* the diet-heart idea! Consider the joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute in their review entitled *The Cholesterol Facts*: "*The results of the Framingham study indicate that a 1% reduction...of cholesterol [corresponds to a] 2% reduction in CHD risk.*"[38]

Please go back to the citation from the Framingham report. Yes, you are right. According to the original report mortality *increased*, and by 11% for each 1mg/dl reduction in blood cholesterol. But the review stated that mortality *decreased*.

Your next thought might be that the distinguished authors of the review referred to another of the numerous reports from Framingham, but they did not. And as we shall see, this was not

their only “mistake.” For example, in 1987, the same authors published a new report concerning the 30 years of follow-up in Framingham.[39] Without presenting anything other than complicated ratios and statistical calculations, and without referring to their previous report, they stated: *“The most important overall finding is the emergence of the total cholesterol concentration as a risk factor for CHD in the elderly.”*

Isn't it strange that the cholesterol liner continues its voyage without any reactions from the passengers or crew? The few who have observed that the ship is leaning are calmed by the captain's assurances that it has only struck an iceberg.[40]

Rule with many exceptions

Most supporters of the diet-heart idea think that the increased risk of coronary heart disease is present at all cholesterol levels. This concept is of course pleasant to the drug producers, for it implies that almost everyone should be treated, including those with a normal cholesterol.

This is not true, however. In most studies, the increased risk is present only above a certain level.[41] As a matter of fact, the relationship between the cholesterol level of the blood and the risk of coronary heart disease seems to be rather unsystematic. Women, for instance, should stop worrying immediately, because high cholesterol is not a risk factor for the female sex.[42] Few words have been aimed at this peculiar fact in the vast literature on cholesterol. When it is mentioned at all, it is said that the female sex hormones protect against heart attacks.

In fact, it seems more dangerous for women to have low cholesterol than high. Together with his team Dr. Bernard Forette, a French researcher from Paris, France, found that old women with a very high cholesterol lived the longest. The death rate was more than five times higher for women with very low cholesterol. The French doctors warned, of course, against lowering the cholesterol in elderly women,[43] but they could as well have warned against cholesterol lowering in any women, or, to be more precise, at all.

It is also notable that whereas high cholesterol has a slight association with increased risk for men in the US, it has no association for men in Canada. This conclusion was reached by Dr. Gilles Dagenais and his team in Quebec after having followed almost 5000 healthy middle-aged men for 12 years.[44] They explained away their surprising finding away by assuming that more than twelve years were needed to see the harmful effect of high cholesterol; obviously they were ignorant of the result from the 30-year follow-up study results.

Neither is blood cholesterol important for those who already had a heart attack. For instance, Dr. Henry Shanoff and his team at the University Hospital of Toronto studied 120 men ten years after their recovery from a heart attack and found that those with low cholesterol had suffered a second one just as often as those with high cholesterol.[45] Many others have confirmed their findings.[46]

In Sweden, Professors Lars-Erik Böttiger and Lars A. Carlson at the Karolinska Hospital found that the risk of coronary heart disease was higher for men with the highest cholesterol, but the risk was considerably lower than in Framingham.[47] They also found that if all kinds of vascular disease caused by atherosclerosis were considered the risk was not increased at all. Those with low cholesterol died as often from vascular disease as those with high.[48]

And there are more exceptions, for instance the Maori people, who originally are Polynesians, but have migrated to New Zealand for several hundred years ago. Unlike the native Polynesians, Maoris often die from a heart attack, but they do it whether their cholesterol is low or high.[49]

In Russia, a *low* cholesterol is associated with an increased risk of coronary heart disease. This was the surprising finding of Dr. Dmitri Shestov from the Russian Academy of Medical Sciences in St. Petersburg. Dr. Shestov and his colleagues, one of them was Professor Herman Tyroler from the Department of Epidemiology at the University of North Carolina, had also analyzed HDL and LDL cholesterol, the “good” and the “bad” cholesterol. They found that a low LDL cholesterol was also associated with an increased risk and this was not due to low levels of HDL-cholesterol. In fact, those with low LDL values had the highest HDL values.[50]

Thus, a high cholesterol is dangerous for Americans but not for Canadians, Stockholmers, or Maoris, and a low cholesterol is dangerous for Russians. A high cholesterol is dangerous for men, but not for women; it is dangerous for healthy men, but not for coronary patients; and it is dangerous for men of thirty, but not for those of forty-eight and may even be beneficial for older people. Such discrepancies indicate that the association between high cholesterol and coronary heart disease is not due to simple cause and effect. The most likely interpretation is that a high cholesterol is not dangerous by itself but a marker for something else.

Many scientists who are critical of the diet-heart idea still have the impression that an increased level of cholesterol in the blood may be dangerous just because of its association with coronary mortality. Few know that the association is unsystematic and even rather weak. And even if the association had been both systematic and strong, this would not prove that it is the high cholesterol level itself that causes atherosclerosis or heart disease. There are at least five other plausible explanations for the higher cholesterol of patients with coronary heart disease.

Guilt by association

Familial hypercholesterolemia is one of them. Individuals suffering from this disease run a greater risk of dying early from a heart attack and they also have a raised cholesterol level. It is a widespread dogma that the increased cholesterol level, by promoting atherosclerosis, is the direct cause of their troubles. But as I shall discuss later it is questionable if the vascular changes seen in familial hyper-cholesterolemia is the same as atherosclerosis.

Smoking generates a slight increase of the blood cholesterol[51] but may induce heart disease by several other mechanisms, for instance by producing many free radicals. Smoking may induce a heart attack *and* an elevated cholesterol level.

Being overweight increases blood cholesterol a little, and weight reduction lowers it a little. Excess weight means an excess burden to the heart. Excess weight may induce a coronary *and* an elevated cholesterol level.[52]

High blood pressure is also associated with changes of blood cholesterol. Hypertension, untreated or treated, is seen in about a third of all individuals with a cholesterol level above 260 mg/dl but only in 15-20 percent of those with a cholesterol less than 220 mg/dl.[53] High blood pressure, or rather the underlying cause, such as stress, may provoke a heart attack *and* raise blood cholesterol.

But the sharpest rise in cholesterol is seen as a result of emotional stress. An academic exam, blood sampling or surgery, conflicts at work or at home, loss of a spouse or a close friend, and various types of performance demands, have been found to increase the cholesterol level by ten to fifty percent.[54] Psychological stress may provoke a heart attack (for instance by spasm of the coronary vessels) *and* an elevated cholesterol level. A likely explanation is that during stress more cholesterol is produced by the liver because cholesterol is used in the manufacture of various stress hormones.

That a high cholesterol is a risk factor for heart disease may have other explanations, but none of them are ever discussed in the papers written by the proponents of the diet-heart idea.

“Look at Finland and Japan”

Perhaps you will ask why it is so scary that death from a heart attack is more common in Western societies, since dying from a heart attack may not be too bad. After all, most of us prefer to die quickly, without spending many years in a nursing home, crippled or senile. And remember that coronary heart disease is a disease of old age. In fact, on average, those who die from a heart attack have lived just as long as other people. Nevertheless, since the association between average blood cholesterol and death rates from coronary disease in various countries has been used as an argument for the diet-heart idea, let us look at some of the facts.

In the Seven Countries study Keys pointed to the association between blood cholesterol and heart mortality. The correlation is obvious, Professor Keys wrote and he illustrated his words with a graph.

It is not apparent from Keys’s paper how the graph is constructed, but it is possible to draw a graph oneself by using the numbers from his tables. I have drawn such a graph choosing the *hard data*, meaning the number who died from coronary heart disease in the various districts, and compared them with the blood cholesterol values (**figure 2B**). If the diet-heart idea is correct heart attacks should, of course, be rare in the districts where cholesterol was low and common where it was high. But as seen from my chart, they were very far from that. Oddly, this important chart is not included in Keys’s paper, although his paper is loaded with more or less relevant graphs.[55]

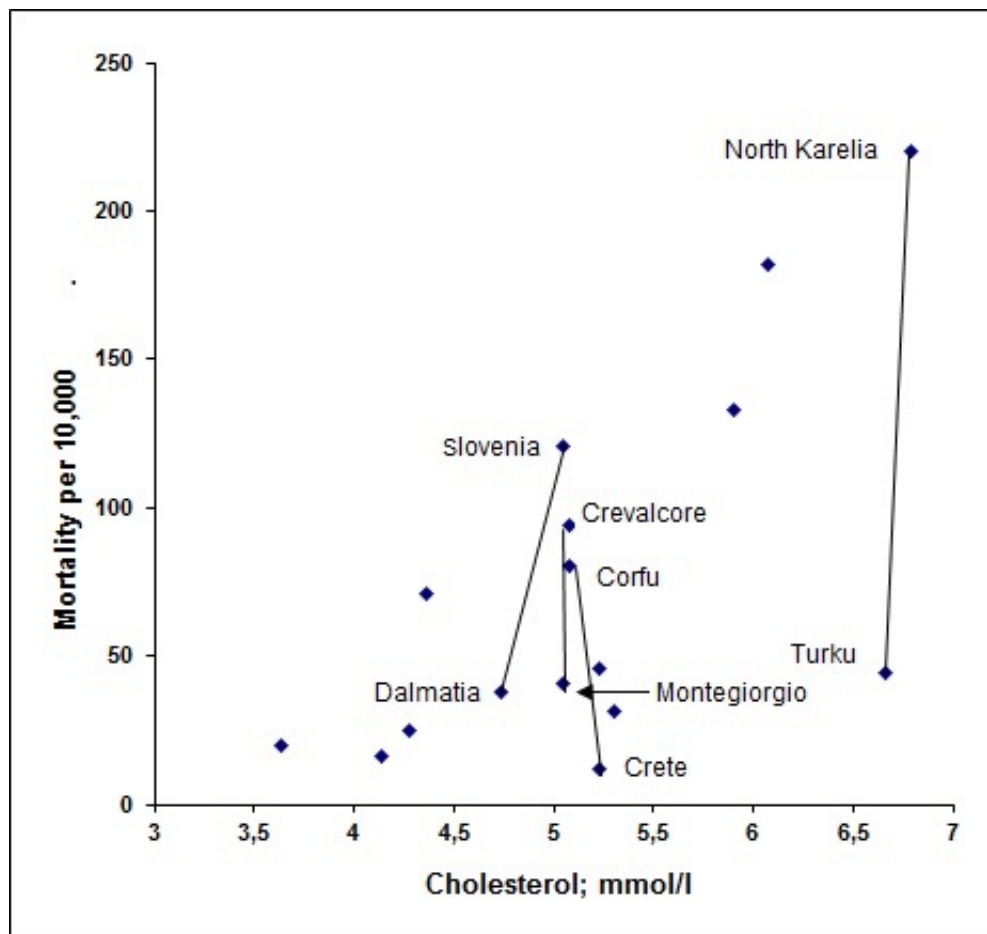


Figure 2B. Five year mortality of coronary heart disease and mean blood cholesterol in 15 populations in the Seven-Countries study. The populations that have been connected with lines are from the same country; see text. The figure is constructed from table data in the report of the Seven-Countries study. Note the great differences in coronary mortality at similar blood cholesterol levels.

There is a notable scattering of the points in the figure. Note for instance that in the districts where fatal heart attacks were uncommon (less than 100 per 100.000) the cholesterol levels vary between the lowest and the second highest value. It is difficult from this figure to see that the number of heart deaths and the level of blood cholesterol are related. Possibly they are statistically related, but we should be skeptical about correlations that depend on just one or two observations. For instance, cover the point labeled Karelen with your hand and the slight impression of an association disappears completely.

Any suggestion of an association also disappears if you look at each country individually (symbols representing various populations in the same country are connected with a line). In Crevalcore, Italy, the number of deaths from heart disease was 2.5 times greater than in Montegiorgio, Italy, although the average blood cholesterol was identical. In Slavonia three times more died from heart disease than in Dalmatia, although the mean cholesterol in Slavonia

was only insignificantly higher. In Finland people living in Karelia died five times more often from a heart attack than people living in the area of Turku although blood cholesterol differed only little. And finally, on the Greek island Corfu people died five times more often from a heart attack than on nearby Crete, although their cholesterol was lower.

If you go to the tables of Ancel Keys's paper again and do a little calculating you will discover another surprising finding: no correlation was found between the diet and the major electrocardiographic findings at entry. Considering that all electrocardiograms were analyzed in the American study center this finding should carry more weight than the correlation with the clinical diagnosis or the diagnosis on the death certificate, settled as they were on location by various physicians with varying competence and diagnostic habits.

But in his conclusion Ancel Keys wrote that the only factor which could explain the great differences between the number of heart attacks in the sixteen areas was the cholesterol level of the blood. And again and again the Seven Countries study is mentioned as a proof of the diet-heart idea: *Look at Finland and Japan*.

Instead, look at the figure once again. It is almost heart-breaking. Eager to prove his hypothesis, Keys unintentionally covered up one of the most interesting tracks. I suspect that many of you already have asked the question that Keys had the opportunity to answer twenty years ago. It is doubtful that the question can be answered so many years later. But, to ask it anyway, what is the factor that protects the inhabitants of Dalmatia, Montegiorgiu, Turku and Crete from coronary heart disease and that is absent in Slavonia, Crevalcore, Karelia and on Corfu?

Or, to turn the question around: why does death from coronary heart disease occur 3-5 times more often in the latter areas? We can blame none of the well-known risk factors because Keys found that they were evenly present in each pair of areas. If Ancel Keys and his coworkers had concentrated all their efforts in these eight places, if they had observed, investigated, questioned and turned every stone upside down they might perhaps have found something helpful to mankind.

This is the most tragic aspect of the cholesterol folly. Interesting side tracks are left unexplored, observations which do not fit with the idea are put aside, and any opportunity for a new discovery is allowed to slip by.

The Japanese Paradox

In Japan cholesterol levels are very low, and few people die from heart disease. This has been known for a long time and was confirmed by the Seven Countries study. Professor Keys also found that Japanese emigrants to the mainland USA had high blood cholesterol and died almost as often from heart attacks as Americans did, while the figures for Japanese emigrants to Hawaii lay somewhere in between.

Professor Keys was convinced that the difference was caused by the food, which in Japan was lean, while on Hawaii, and especially in the continental US, it was rich in animal fat.[\[56\]](#)

As usual Keys had no other explanation. And what he did not mention was that while coronary mortality increased after the Japanese had migrated to the US, stroke mortality decreased just as much and total mortality decreased much more.[\[57\]](#)

There is an alternative explanation to the increased coronary mortality after migration from Japan to the US.

As I mentioned earlier, calories from animal fat are usually expensive, and such food is therefore mostly consumed in rich countries, such as the Western, industrialized nations.

Calories from carbohydrates and vegetable oils are cheaper and such food therefore predominates in poor countries with a low degree of industrialization and a low standard of living. When Ancel Keys gathered his data in the early 1960s Japan belonged to this category. It was still a poor nation, successfully recovering from war, not the rich nation triumphant in industry that we know today.

Immigrants from a poor country are exposed in their new, richer country to many other things besides high-fat food. A multitude of factors in the Western environment or lifestyle may adversely effect the heart and the blood vessels, such as less physical activity, more stress, and more environmental and industrial pollutants.

In his doctoral thesis about coronary heart disease in Japanese immigrants, British physician Dr. Michael Marmot presents some interesting insights into the relationship between blood cholesterol levels and social factors, eating habits and lifestyle.[\[58\]](#) Dr. Marmot demonstrated that it was not the food that raised the cholesterol of the Japanese immigrants, nor high cholesterol values that increased their risk of coronary heart disease. He found that if they maintained their cultural traditions, they were protected against heart attacks, even though their cholesterol increased as much as in Japanese immigrants who adopted a Western lifestyle and who died from heart attacks almost as often as did native-born Americans. The most striking of Dr. Marmot's findings was that *emigrants who maintained the Japanese traditions but preferred high-fat American food ran a smaller risk of heart disease than those who became accustomed to the American way of life but ate the lean, Japanese food.*

Thus, according to Dr. Marmot's study, there is something in the Japanese way of living that protects against coronary heart disease, and it is not the food.

Dr. Marmot himself points to the traditional Japanese culture, which is still a major factor shaping life in present-day Japan. In particular, the Japanese place great emphasis on group cohesion, group achievement, and social stability. Members of the stable Japanese society enjoy support from other members of their society and thus are protected from the emotional and social stress that Marmot believes to be an important cause of heart attacks. The Japanese traditions of togetherness contrast dramatically with the typical American emphasis on social and geographic mobility, individualism, and striving ambition.

Ignoring embarrassing data

We do not know whether Dr. Marmot's explanation is correct or not. However, if his *findings* are correct, the diet-heart idea must be wrong. But Dr. Marmot's results, as well as the many other embarrassing contradictory findings, have been ignored in the official reviews.

In 1979 for instance, the American Health Foundation organized an international conference with the aim of finding "the optimal cholesterol level." In a later step, the level was to be lowered in the countries where the conference participants thought it was too high. The written

report from this conference[59] presented a meticulous account of Dr. Marmot's results including detailed information about the Japanese food, cholesterol levels and risk of heart disease. But Marmot's message (and the epidemiological data on which it was founded), was ignored.

Let's look at a few more examples of the researchers sweeping contradictory findings under the rug. A large review written in 1984 by Dr. William Kannel, head of the Framingham project, and his colleagues, stated that *there is a strong association between population means of total cholesterol and CHD incidence*, and here Dr. Kannel refers to Ancel Keys's Seven Countries study.[60] (*Total cholesterol* simply means cholesterol. The term *total cholesterol* is used in texts where subfractions such as LDL- and HDL-cholesterol are also mentioned.)

The largest review, *Diet and Health*, published in 1989, comes from the prestigious *National Research Council* and concluded as follows:

“Epidemiological findings among populations and for individuals within populations consistently indicate a strong, continuous, and positive relationship between TC [Total Cholesterol] levels and the prevalence and incidence of, as well as mortality from, atherosclerotic CHD.”[61]

Many supporters of the diet-heart idea seem to have stopped thinking critically. Perhaps, as members of a worldwide alliance that includes many distinguished researchers, they have become overconfident, too willing to assume that an idea must surely be valid if great numbers of people endorse it.

But if they were familiar with the way science has progressed through the centuries, they would know that the truth cannot be ruled out by the majority or decreed by consensus.

Another myth: “good” and “bad” cholesterol

Cholesterol is a peculiar molecule. It is often called a lipid or a fat, but the chemical term for a molecule such as cholesterol is alcohol, although it doesn't behave like alcohol. Its numerous carbon and hydrogen atoms are put together in an intricate three-dimensional network, impossible to dissolve in water. All living creatures use this indissolubility cleverly, incorporating cholesterol into their cell walls to make cells waterproof. This means that cells of living creatures are able to regulate their internal environment undisturbed by chemical changes in the surrounding milieu. The fact that cells are waterproof is especially critical for normal functioning of nerves and nerve cells. Thus, the highest concentration of cholesterol in the body is found in the brain and other parts of the nervous system.

Because cholesterol is insoluble, it circulates in the blood inside spherical particles composed of fats (lipids) and proteins, the so-called lipoproteins. Lipoproteins are easily dissolved in water because their outside is composed mainly of water-soluble proteins. The inside of the lipoproteins is composed of lipids, and here we have room for water-insoluble molecules like cholesterol. Like submarines, lipoproteins carry cholesterol from one place in the body to another.

These submarines, or lipoproteins, are categorized according to their density. The best known are HDL (High Density Lipoprotein), and LDL (Low Density Lipoprotein).

The main task of HDL is to carry cholesterol from the peripheral tissues, including the artery walls, to the liver. Here it is excreted with the bile, or used for other purposes, for instance as a starting point for the manufacture of important hormones.

The LDL submarines mainly transport cholesterol in the opposite direction. They carry it from the liver, where most of our body's cholesterol is produced, to the peripheral tissues, including the artery walls. When cells need cholesterol, they call for the LDL submarines, which then deliver cholesterol into the interior of the cells.

Between 60 and 80 percent of the cholesterol in the blood is transported by LDL and is called “bad” cholesterol. Only 15-20 percent is transported by HDL and is called “good” cholesterol. A small part of the circulating cholesterol is transported by other lipoproteins.

You may ask why a natural substance in our blood with important biologic functions, is called “bad” when it is transported from the liver to the peripheral tissues by LDL, but “good” when it is transported in the other direction by HDL. The reason is that a number of follow-up studies have shown that a lower-than-normal level of HDL-cholesterol and a higher-than-normal level of LDL-cholesterol are associated with a greater risk of having a heart attack, and conversely, that a higher-than-normal level of HDL-cholesterol and a lower-than-normal LDL-cholesterol are associated with a smaller risk. Or, said in another way, a low HDL/LDL ratio is a risk factor for coronary heart disease.

By now you know that a risk factor is not necessarily the same as the cause, and that something may provoke a heart attack and at the same time lower the HDL/LDL ratio. Let us have a look at some factors known to influence this ratio.

The cholesterol ratio caper

As mentioned above, people who reduce their body weight also reduce their cholesterol. A review of 70 studies showed that, on average, weight reduction lowers cholesterol by about 10 percent, depending on the amount of weight loss. Interestingly, it is only cholesterol transported by LDL that goes down; the small part transported by HDL goes up. In other words, weight reduction increases the ratio between HDL and LDL-cholesterol.

An increase of the HDL/LDL ratio is called *favorable* by the diet-heart supporters; cholesterol is changed from “bad” to “good.” But is it the ratio or the weight reduction that is favorable? When we become fat, other harmful things occur to us. One is that our cells may become less sensitive to insulin, so that some of us even develop diabetes. And people with diabetes are much more likely to have a heart attack than people without diabetes, because atherosclerosis and other vascular damage may occur early in diabetics, even in those without lipid abnormalities. In other words, overweight may increase the risk of a heart attack by mechanisms other than an unfavorable lipid pattern, while at the same time overweight lowers the HDL/LDL ratio.

You may also recall that smoking increases cholesterol a little. Again, it is LDL-cholesterol that increases, while HDL-cholesterol goes down, resulting in an *unfavorable* HDL/LDL ratio. What is certainly unfavorable is chronic exposure to the fumes from H paper and tobacco leaves. It should be obvious that instead of considering a low HDL/LDL ratio as bad, we should consider the possibility that smoking in and of itself is bad. Smoking may provoke a heart attack and, at the same time, lower the HDL/LDL ratio.

Exercise decreases the so-called bad LDL-cholesterol and increases the so-called good HDL-cholesterol.[62] In well-trained individuals the good HDL is increased considerably. In a comparison between distance runners and sedentary individuals, Dr. Paul D. Thompson and his team from Providence, Rhode Island, found that the athletes on average had a 41 percent higher HDL-cholesterol level.[63] Most population studies have shown that physical exercise is associated with a lower risk of heart attacks and a sedentary life with a higher risk. A well-trained heart is better guarded against obstruction of the coronary vessels than a heart always working at low speed simply because the vascular channels in the well-trained heart are broader; remember the wide coronary arteries of the Masai people who ran all day long after their cattle in Kenya. A sedentary life may predispose people to a heart attack and, at the same time, lower the HDL/LDL ratio.

Univariate and multivariate

Thus, the risk of having a heart attack is greater than normal for people with high LDL-cholesterol, but so is the risk for fat, sedentary and smoking individuals. And since such individuals usually have elevated levels of LDL cholesterol, it is, of course impossible to know whether the increased risk is due to the previously mentioned risk factors (or to risk factors we do not yet know) or to the high LDL-cholesterol. A calculation of the risk of high LDL-cholesterol that does not consider other risk factors is called a univariate analysis and is, of course, meaningless.

To prove that high LDL-cholesterol is an independent risk factor, we should ask if fat, sedentary, smoking individuals with a high LDL-cholesterol level are at greater risk for coronary disease than fat, sedentary, smoking individuals with low or normal LDL-cholesterol.

Using complicated statistical formulas, it is possible to do such comparisons in a population of individuals with varying degrees of the risk factors and varying levels of LDL-cholesterol, a so-called multivariate analysis. If a multivariate analysis of the prognostic influence of LDL-cholesterol also takes body weight into consideration, it is said to be *adjusted for body weight*.

A major problem with such calculations is that we know a great number of risk factors, but not all of them. Another problem is that the data generated by these and other complicated statistical methods are almost impossible for most readers, including most doctors, to comprehend. For many years researchers in this area have not presented primary data, simple means, or simple correlations. Instead, their papers have been salted with meaningless ratios, relative risks, p-values, not to mention obscure concepts such as *the standardized logistic regression coefficient*, or *the pooled hazard rate ratio*. Instead of being an aid to science, statistics are used to impress the reader and cover the fact that the scientific findings are trivial and without practical importance. Nevertheless, let us have a look at some of the studies.

The “good” one

Publications almost beyond counting have studied the prognostic value of the “good” HDL cholesterol. The reason is, of course, that it is hard to find any prognostic value. If HDL-cholesterol had a heart-protecting effect of real importance, it would not be necessary to use the taxpayers’ money to demonstrate the effect again and again in expensive studies. To be brief I shall tell you only about a few of the largest studies.

In 1986 Dr. Stuart Pocock and his team from London and Birmingham, England published a report concerning more than 7000 middle-aged men in 24 British towns.[64] The men had been followed for about four years after a detailed analysis of their blood. During this period 193 of the men had suffered a heart attack. As in most previous studies, these men had on average a lower HDL-cholesterol at the beginning than the men who did not have a heart attack. The mean difference between the cases and the other men was about 6 percent. This difference was small of course, but thanks to the large number of individuals studied it was statistically significant.

But this was a univariate analysis and as mentioned, the difference could therefore be explained in many ways. A multivariate analysis adjusted for age, body weight, cigarette smoking and non-HDL-cholesterol reduced the difference to an insignificant 2 percent. This means that those who had suffered a heart attack had a lower HDL-cholesterol mainly because they were older, fatter and smoked more than those who had not had a heart attack.

The British scientists compared their findings with those of six other studies. In five of them the differences were just as small. Only one study found a considerable difference, but it included 39 individuals only and thus was highly susceptible to bias. Dr. Pocock and his colleagues concluded that a low HDL-cholesterol level is not a major risk factor for coronary heart disease.

Their results were challenged in 1989 by nine American scientists headed by Dr. David Gordon at the National Heart, Lung and Blood Institute. They had analyzed the predicative value of HDL-cholesterol in four large American studies, including more than 15,000 men and women. [65] They thought that the British scientists had used an incorrect way to adjust their figures. Using another formula, the American researchers wrote, showed HDL-cholesterol to be a much better predictor.

But in one of the four studies the number of fatal heart attacks was identical in the first and second HDL tertile (individuals were classified into three groups, or tertiles, according to their HDL-cholesterol). In one of the studies the number of fatal cases was identical in the second and the third tertile, and in one study more deaths were seen in the third tertile (those who had the largest amount of the “good” cholesterol) than in the second tertile. And these figures were the unadjusted ones.

After adjustment the differences were even smaller. In three of the four studies, the differences lost statistical significance. And remember that the figures were not adjusted for physical activity, not to mention the risk factors we do not know yet.

Dr. Pocock and his colleagues returned with a new analysis later the same year, now using the same way of analyzing as had Dr. Gordon and his colleagues. At that time the participants in the study had been followed for 7.5 years and a total of 443 heart attacks had occurred.[66]

This time a difference was noted between the HDL-cholesterol of the heart patients and the others. The difference was small but statistically significant, even after adjustment. However, *the largest difference was noted for total cholesterol*. The authors therefore concluded that a determination of HDL-cholesterol may be of marginal additional value in screening and in intervention programs for risk of coronary heart disease. They could also have added that they did not adjust for all risk factors so that the difference could as well be due to the heart patients being, for instance, more stressed or less active physically than the others.

And even if the difference had remained after adjustment of all the known risk factors the crucial question is if HDL-cholesterol has any importance whatsoever. From what you have read till now and especially from the chapters to come, you will realize that there is little or no evidence, that blood cholesterol plays a role in coronary heart disease. If total cholesterol, a better predictor than HDL-cholesterol, is unimportant, how could HDL-cholesterol be important?

I am tempted to discuss the many other studies which did not find HDL-cholesterol a good predictor. But to avoid boring you, I shall mention only the 24-year follow-up of the Finnish group in the Seven Countries study, because this is one of the longest follow-up studies of HDL-cholesterol.^[67] A total of 518 healthy men from three areas in Finland were followed. **Table 2A** gives the number of fatal heart attacks and the starting average HDL-cholesterol in each area.

Table 2A. Mean HDL-cholesterol in three Finnish areas and coronary mortality 24 years later.

| Country | Initial HDL-cholesterol (mg/dl) | Mortality from Coronary heart disease Per 1000 men 24 years later |
|---------------|---------------------------------|---|
| Helsinki | 44.8 | 81 |
| West Finland | 43.2 | 105 |
| North Karelia | 47.6 | 183 |

If HDL cholesterol were good for the heart, the smallest number of men should have died from heart attacks in North Karelia, where HDL-cholesterol was the highest. Instead, the number was twice as large as in Helsinki.

In their paper, Keys and his co-authors mentioned two equally large and long-lasting studies that also found lower HDL-cholesterol in the healthy survivors than in those who had died from coronary disease. But in the summary of the paper they wrote: *“These 24-year findings are not necessarily in conflict with reports in the literature on an inverse relationship between coronary heart disease incidence and HDL cholesterol.”*

It is fortunate that low HDL-cholesterol itself does not increase the risk of a heart attack, because the prudent diet has a surprising effect on the HDL-cholesterol level. A French study by Dr. Frédéric Fumeron and his colleagues in Paris and Lille investigated the effect of two different diets on 36 healthy individuals. One diet contained 70 grams of butter, the other 70 grams of sunflower margarine; otherwise the diets were similar. Each individual ate both diets for three weeks; half of them started with the butter diet, half with the “prudent” margarine diet.^[68]

As in many previous studies, analysis of the blood lipid levels before and after each period showed that the “prudent” diet lowered blood cholesterol. But it also lowered the “good” HDL-cholesterol, especially two of its subfractions called HDL-2 and LpA-I. Other studies have

shown that these subfractions are especially “good.” The authors also reviewed seven other studies with similar results.

The “bad” one

LDL has the strongest and most consistent relationship to individual and population risk of CHD, and LDL-cholesterol is centrally and causally important in the pathogenetic chain leading to atherosclerosis and CHD. These words you will find in the large review *Diet and Health*.

A scientific review is, like this book, an analysis of what has been done and what has been written about a certain subject. Reviews usually do not present observations or experiments performed by the authors themselves. Reviews help researchers by sparing them the tedious work of seeking the primary observations themselves in the library or in the electronic data bases. Furthermore, in their papers researchers can refer to a few reviews instead of to a large number of original works. But, of course, the researcher must be sure that the reviews are complete and correct and that they give a balanced view.

Reviews by distinguished scientific bodies are supposed to meet such standards. Therefore, you are probably wondering how the authors of *Diet and Health* had reached their conclusion about LDL-cholesterol. I wondered too, when I started to untangle the HDL-LDL issue,[\[69\]](#) because extensive reading had not yet given me the answer.

The fact is that very few analyses of LDL-cholesterol have been published. For example, in the hundreds of reports from the Framingham study very little is mentioned about LDL-cholesterol. An odd fact because all participants had this cholesterol fraction measured at the start and again later in the study.

Diet and Health is the official, most authoritative and supposedly most reliable review from the National Research Council in Washington. I was confident that its highly qualified authors would have the answer. What was their evidence? Upon which observations or experiments did they base their statements about the dangers of LDL-cholesterol?

Diet and Health cites four publications. First, in 1973 Dr. Jack Medalie and his team at the Tel Aviv University in Israel published a five-year follow-up study of 10,000 Israeli male government and municipal employees.[\[70\]](#) Among a large number of factors relevant to the study of coronary heart disease they had measured total and LDL-cholesterol. According to *Diet and Health* LDL cholesterol has the strongest relationship to risk of heart disease. However, the Israeli study did not support these words, because *total* cholesterol, not LDL-cholesterol, had the strongest relationship to risk of coronary disease.

The second paper claimed by the *Diet and Health* authors to support the idea about the dangerous LDL cholesterol, was a 1977 report from the Framingham Study.[\[71\]](#) This study concerned HDL cholesterol, however. Only logistic regression coefficients (a statistical concept unknown to most doctors) for coronary disease on LDL-cholesterol were given, and one of the conclusions of the paper was that *LDL-cholesterol... is a marginal risk factor for people of these age groups* (men and women above 50 years). Some of the coefficients were indeed low. For women above the age of 70 it was negative, which means that women at that age ran a

greater risk of having a heart attack if their LDL-cholesterol was low than if it was high. Thus, there was no support either from that paper.

Also the third paper[72] concerned HDL-cholesterol only. Thus, no support either.

The fourth reference was to the *National Cholesterol Education Program*, which produced another large review without original data.[73] One of its conclusions was that, “a large body of epidemiological evidence supports a direct relationship between the level of serum total and LDL-cholesterol and the rate of CHD.” I became excited, thinking, “At last, the evidence.”

The large body of evidence was to be found in three references. The first one was another large review without original data, *Optimal resources for primary prevention of atherosclerotic disease*,[74] with Dr. Kannel as the first author. I shall return to their review.

The next reference was yet a large review,[75] but nothing in that review was said about the matter.

The last reference was a report from the Honolulu Heart Study.[76] The conclusion of that paper was that, “both measures of LDL-cholesterol were related to CHD prevalence, but neither appeared to be superior to total cholesterol.”

Before I discuss Dr. Kannel’s review I shall mention another conclusion in the *National Cholesterol Education program*: “The issue of whether lowering LDL-cholesterol levels by dietary and drug interventions can reduce the incidence of CHD has been addressed in more than a dozen randomized clinical trials.” This is a most misleading statement because at that time, in 1988, only four such trials had included an LDL-cholesterol analysis,[77] and only in one of them the number of heart attacks was lowered significantly.

Let me now return to the review by Dr. Kannel and colleagues, the one used as evidence by the authors of the *National Cholesterol Education Program*, which in turn was used as evidence by the authors of *Diet and Health*. Almost nothing was written about LDL-cholesterol in Dr. Kannel’s review except for the following: “Longitudinal studies within populations show a consistent rise in the risk of CHD in relation to serum total cholesterol and LDL-cholesterol at least until late middle-age.”

A little more cautious conclusion than in *Diet and Health*, it may seem, but even for this prudent statement the evidence was weak. References to six studies were given. In two of them LDL-cholesterol was not analyzed or mentioned at all.[78] In two reports LDL-cholesterol was only correlated to the prevalence of heart disease, which means that it was not a longitudinal study.[79] In one report two tables were aimed at the subject (tables 8 and 9) and showed that the predictive power of LDL-cholesterol was statistically non-significant.[80] In one study LDL-cholesterol was predictive for heart disease, but only for men between 35 and 49 and only for women between 40 and 44.[81]

In conclusion, the “large body of evidence” can be reduced to one single study, which showed a predictive value for LDL-cholesterol but for a few age groups only. The only valid conclusion therefore is that LDL-cholesterol is *neither* centrally *nor* causally important, it has *not* the strongest and most consistent relationship to risk of CHD, it has *not* a direct relationship to the rate of CHD, and it has *not* been studied in more than a dozen randomized trials.

You can read more about the above in one of my papers.[\[82\]](#)

Familial hypercholesterolemia—not as risky as you may think

Many doctors believe that most patients with familial hypercholesterolemia (shortened FH) die from CHD at a young age. Obviously they do not know the surprising finding of a Scientific Steering Committee at the Department of Public Health and Primary Care at Ratcliffe Infirmary in Oxford, England.[\[83\]](#) For several years, these researchers followed more than 500 FH-patients between the ages of 20 and 74 for several years and compared patient mortality during this period with that of the general population.

During a three-to-four-year period, six of 214 FH-patients below age 40 died from CHD. This may not seem particularly frightening, but as it is rare to die from CHD before the age of 40, the risk for these FH patients was almost 100 times that of the general population.

During a four-to-five-year period, eight of 237 FH-patients between ages 40 and 59 died, which was five times more than in the general population. But during a similar period of time, only one of 75 FH-patients between the ages of 60 and 74 died from CHD.

If these results are typical for FH, you could say that, between ages 20 and 59, about three percent of the patients with FH died from CHD, and between ages 60 and 74, less than two percent died from CHD, fewer than in the general population.

The authors stressed that the patients had been referred because of a personal or family history of premature vascular disease and therefore were at a particularly high risk for CHD. Most patients with FH in the general population are unrecognized and untreated. Maybe the prognosis of the Oxford patients would have been even better if they had been representative for all FH patients?

Dr. Eric Sijbrands and his coworkers from various medical departments in Amsterdam and Leiden, Netherlands have the answer. The Dutch researchers screened a large number of healthy people and found three individuals with very high cholesterol. A genetic analysis confirmed the diagnosis of FH and by tracing their family members backwards they came

up with a total of 412 individuals. The coronary and total mortality of these members were compared with the mortality of the general Dutch population.

The striking finding was that the FH people had a normal mortality during the nineteenth and early twentieth century; in fact, mortality was even lower than in the general population during the nineteenth century. After 1915 the mortality rose to a maximum between 1935 and 1964, but even at the peak it was less than twice as high as in the general population.[\[84\]](#)

Again, very high cholesterol does not lead to a heart attack by itself. High cholesterol may even be protective against other diseases. This was the conclusion of Dr. Sijbrands and his colleagues. As support they mentioned that genetically modified mice with high cholesterol are protected against severe bacterial infections.

“Don’t be afraid, doctor, but my cholesterol is very high.” These were the words of a 50-year old lawyer who visited me for the first time for a health examination. And indeed, his cholesterol was high, over 400 mg/dl (10.3 mmol/l).

“But my father’s cholesterol was even higher,” he added. “He lived happily until he died at age 79 from cancer. And his brother, who also had FH, died at age 83. None of them ever complained of any heart problems.”

My “patient” is now 53, his brother is 56 and his cousin 61. All of them have extremely high cholesterol values, but none of them has any heart troubles, and none of them has ever taken cholesterol-lowering drugs.

So, if you happen to have FH, don’t be too anxious. Your chances of surviving are pretty good, even surviving to old age.

Myth 3: High-Fat Foods Raise blood Cholesterol

Ye shall eat the fat of the land.

Genesis 45:18

Food and fat in various populations

Why do levels of cholesterol vary in different people? Because of their food! This is the answer from Ancel Keys, stated over and over again in his papers. No alternative explanations are ever mentioned; Keys's hand never trembles when he writes about the influence of diet on blood cholesterol.

One of his arguments is that the average blood cholesterol is high in countries where people eat lots of high-fat food, especially foods high in animal fat, and low in countries where people eat little fat. And, asserts Keys, if an individual with low cholesterol moves to an area where people's cholesterol is high, then his cholesterol will also rise.

In 1958 Keys illustrated his idea with a diagram demonstrating the relationship between the amount of fat in the food and the cholesterol level of the blood in various populations (fig. 3A).[\[86\]](#)

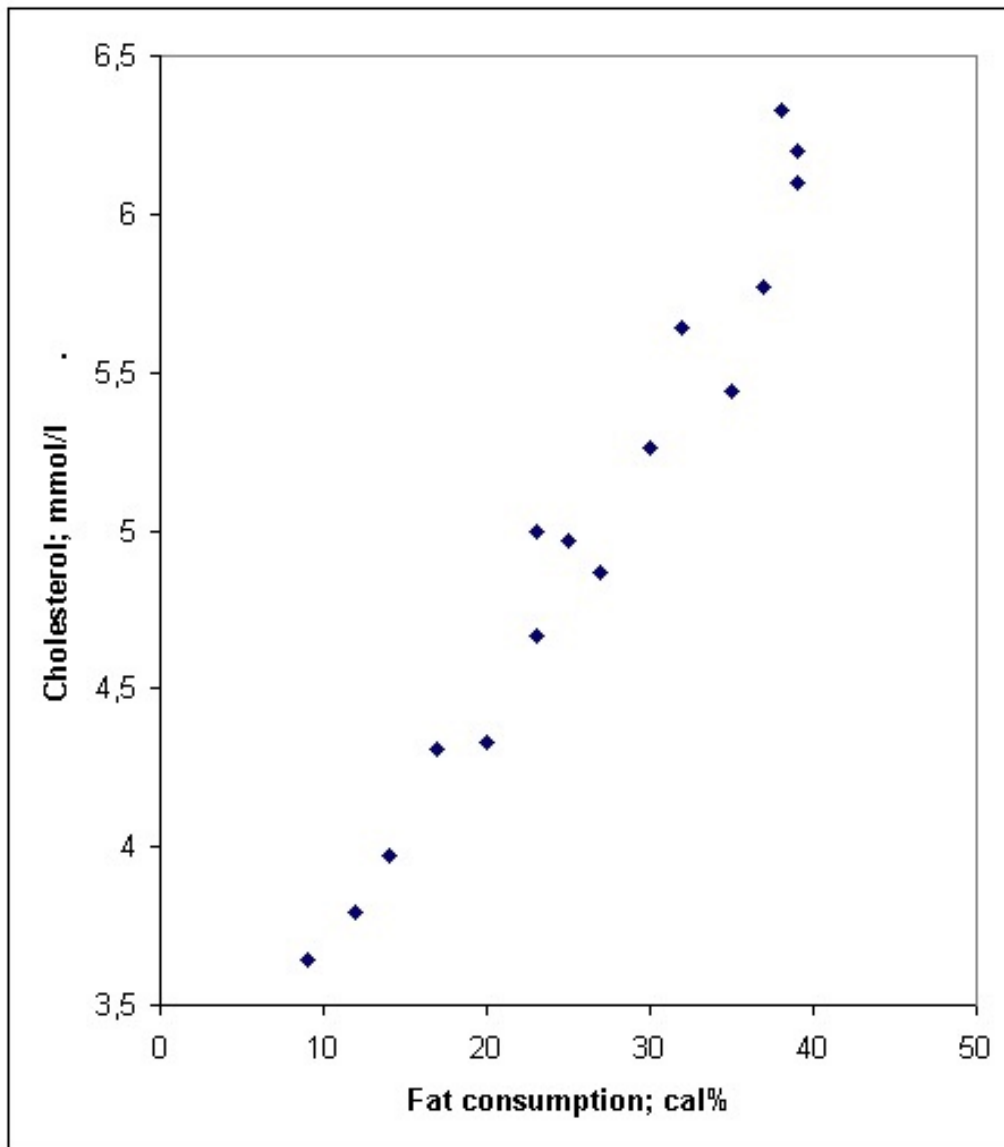


Figure 3A. Correlation between dietary fat and blood cholesterol in various populations. After Keys.

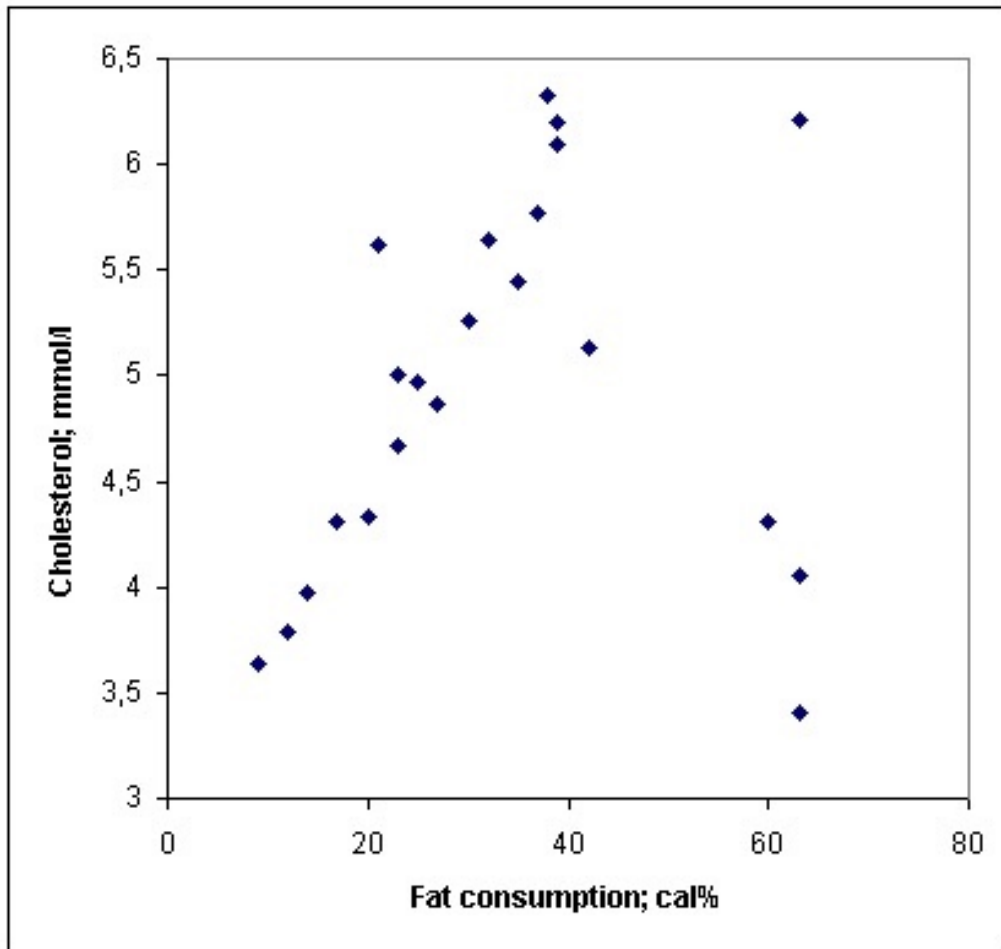


Fig. 3B. Same diagram as figure 3A, but including populations that Keys had ignored.

It is possible to draw an even curve through almost all points, an amazing result considering the uncertainties associated with the figures behind the individual points. It is highly unusual to find such a strong correlation in medical or biological science because observations of living creatures are much more imprecise than observations in physics and chemistry.

Note also that the figure gives the blood cholesterol related to the *total* amount of dietary fat. In his later study Seven Countries Professor Keys claimed that the correlation is far better if cholesterol is related to the intake of *animal* fat. Possibly you wonder how it could be better than shown in figure 3A. The reason is that in Seven Countries Keys found no correlation at all between total fat and heart mortality.

How come that in the first study Keys found a strong correlation, but in Seven Countries there was no correlation at all? The explanation is that in his first study Keys had ignored some remarkable populations.

Camels, cows and cholesterol

I have already discussed the discrepancies between the low blood cholesterol of the Masai and the Samburu cattle herders and their rich, high-fat food. Why didn't Keys include the Samburu people in his elegant diagram? Wasn't it interesting that for long periods they drank almost two gallons of milk each day. Milk from the African Zebu cattle is much fatter than our cow's milk, which means that the Samburus consume more than twice the amount of animal fat than the average American, and yet their cholesterol is much lower, about 170 mg/dl (4.36 mmol/l).[\[86\]](#)

Shepherds in Somalia eat almost nothing but milk from their camels. About a gallon and a half a day is normal, which amounts to almost one pound of butter fat, because camel's milk is much fatter than cow's milk.

But although more than sixty percent of their energy consumption comes from animal fat, their mean cholesterol is only about 150 mg/dl (3.85 mmol/l), far lower than that of most Western people.[\[87\]](#)

Cholesterol and coconuts

Dr. Ian Prior and his team from Wellington, New Zealand, studied the population of the Tokelau Islands and the Pukapuka atolls.[\[88\]](#) Here the main food is coconuts prepared in various ways, but seafood and chicken are also on the menu. Coconuts contain great amounts of coconut butter. Unlike most other types of vegetable fat coconut butter has a high content of saturated fatty acids, even higher than in animal fat.

On the Tokelau Islands the amount of saturated fat was almost twice that of Pukapuka and even higher than in the US, while the consumption of polyunsaturated oil was small on all islands.

The scientists confirmed that the Polynesian people really ate this great amount of saturated fatty acids by analyzing the fat beneath their skin. With a syringe they sucked out a little of this fat and found that its content of saturated fatty acids was twice that of Western people. Also, the chickens these Pacific islanders ate had a high content of saturated fatty acids in their tissue, probably because they ate a considerable amount of coconut.

The cholesterol of the Tokelauans was higher than that of the Pukapuka inhabitants as expected according to the diet-heart idea, but it was at least 20 percent lower than it should have been if Keys's calculations were correct. Now to the most interesting point.

In 1966 a tornado pulled up a great number of coconut trees on the islands. The atolls could no longer feed their inhabitants and one thousand Tokelauans migrated to New Zealand. In New Zealand their diet changed markedly; the amount of calories from saturated fat was halved while the intake of polyunsaturated fat increased a little.[\[89\]](#)

Here was the perfect opportunity to prove the diet-heart hypothesis, but the results of this so-called "favorable" change in diet did not live up to expectations. Instead of going down as

expected, the cholesterol of the Tokelauans increased by about 10 percent as seen in Table 3A.

Table 3A. Fat content of the food of Tokelau inhabitants and Tokelau emigrants in New Zealand, and their blood cholesterol level.

| | Tokelau | New Zealand |
|-----------------------------------|----------------|--------------------|
| Proportion energy (%) from | | |
| saturated fat | 45% | 21% |
| polyunsaturated fat | 3% | 4% |
| Blood cholesterol (mg/dl) | | |
| men, 45-54 years | 195 mg/dl | 219 mg/dl |
| women, 45-54 years | 213 mg/dl | 225 mg/dl |

Thus, something in the environment or lifestyle in New Zealand had such a great impact of the Tokelauans that their cholesterol increased, although their consumption of saturated fat was reduced by half.

Experiments and reality

Another of Keys's arguments derives from the results of laboratory experiments to lower cholesterol by diet. The experiments are summarized as follows.

If energy is supplied mainly by saturated fatty acids, those dominating in animal fat and in coconut butter, blood cholesterol goes up a little.

If energy is supplied mainly by polyunsaturated fatty acids, those dominating in most vegetable fat and fat from seafood, blood cholesterol goes down a little.

Oddly, cholesterol in the diet has only a marginal influence on the cholesterol in the blood. The explanation is that we regulate our own production of cholesterol according to our needs. When we eat much cholesterol, the body's production goes down; when we eat only little, it goes up.

The fact that a suitable diet may change the blood cholesterol level has been demonstrated by the cholesterol-lowering trials. An extreme diet may lower the level by about ten percent; a more palatable diet only a few percent.[\[90\]](#)

Now to one of the cholesterol paradoxes. Although it is possible to change blood cholesterol a little in laboratory experiments and clinical trials by dieting, it is impossible to find any relationship between the make up of the diet and the blood cholesterol of individuals who are not participating in a medical experiment. In other words, individuals who live as usual

and eat their food without listening to doctors or dieticians show no connection between what they eat and the level of their blood cholesterol.

If the diet-heart idea were correct individuals who eat great amounts of animal fat would have higher cholesterol than those who eat small amounts; and individuals who eat small amounts of vegetable fat should have higher cholesterol than those who eat great amounts. If not, there is no reason to meddle with people's diet.

Counting money and counting food

Even in the early 1950s the Framingham study included dietary analyses. Almost one thousand individuals were questioned in detail about their eating habits. No connection was found between the composition of the food and the cholesterol level of the blood. Wrote Drs. William Kannel and Tavia Gordon, authors of the report: *"These findings suggest a cautionary note with respect to hypotheses relating diet to serum cholesterol levels. There is a considerable range of serum cholesterol levels within the Framingham Study Group. Something explains this inter-individual variation, but it is not the diet."*

For unknown reasons, their results were never published. The manuscript is still lying in a basement in Washington.[\[91\]](#)

In a small American town called Tecumseh, Michigan a similar study was performed by a team of researchers from the University of Michigan headed by Dr. Allen Nichols. Experienced dieticians asked in great detail more than two thousand individuals what they had eaten during a twenty-four hour period. The dieticians also asked about the ingredients of the food, analyzed the recipes of home-cooked dishes, and exerted great care to find out what kind of fat was used in the kitchen. Calculations were then performed using an elaborate list of the composition of almost 3000 American food items. Finally the participants were divided into three groups, a high, a middle, and a low level group, according to their blood cholesterol.

No difference was found between the amounts of any food item in the three groups. Of special interest was that the low-cholesterol group ate just as much saturated fat as did the high-cholesterol group.[\[92\]](#)

These studies concerned adults, but no association has been found in children either. At the famous Mayo Clinic in Rochester, New York, for instance, Dr. William Weidman and his team analyzed the diet of about one hundred school children. Great differences were found between the amount of various food items eaten by these children, and also great differences between their blood cholesterol values, but there wasn't the slightest connection between the two. The children who ate lots of animal fat had just as much or just as little cholesterol in their blood as the children who ate very little animal fat.[\[93\]](#)

A similar investigation of 185 children was performed in New Orleans with the same result.[\[94\]](#)

Even if no pains are spared to investigate the diet of people the information gathered is of course uncertain. Who can recall everything that he has eaten in the last twenty-four hours?

And the diet of one 24-hour period may not be representative of the usual diet of the individual. A better result can be achieved by studying the diet over several days, preferably during various seasons of the year. In London professor Jeremy Morris and his team used this method and asked ninety-nine middle-aged male bank staff members to weigh and record what they ate over two weeks.

Have you ever bargained in a bank? Maybe you will succeed in the director's office, but certainly not at the teller's counter. If anyone is scrupulous with nickels and dimes, it is those sitting behind the glass of the bank.

Ninety-nine of these honorable men were asked to sit at home with a letter balance and weigh every morsel they ate for a whole week. But again, this meticulous method revealed no connection either between the food and the blood cholesterol level.

To be certain, seventy-six of the bank men repeated the procedure for another week at another time of the year: no connection was found, once again.

To be absolutely certain the researchers selected those whose records were especially detailed and accurate. Once more, no connection was found.[\[95\]](#)

Another look at Finland

On average Finnish people have the highest cholesterol in the world. According to the diet-heart idea's proponents, this is due to the fat-rich Finnish food. The answer is not that simple, however. This was demonstrated by Dr. Rolf Kroneld and his team at the University of Turku.[\[96\]](#)

They studied all inhabitants of the village of Iniö near Turku, and twice as many randomly selected individuals of the same age and sex in North Karelia and in southwest Finland.

Apparently a health campaign had struck Iniö. There the consumption of margarine was twice as great and the consumption of butter only half as what it was in the other places. Also, the people of Iniö preferred skimmed over whole milk; the residents of the other districts did not. But the highest cholesterol values were found in Iniö.

The average value for male Iniö inhabitants was 283 mg/dl, on the two other places it was 239 and 243 mg/dl. Regarding women, the difference was even greater.

Threshold on trial

Is it really wise to meddle with people's dietary habits if their food has no influence on their cholesterol? And how do those who believe that fat food is dangerous explain all these negative results?

Most often they argue that information about dietary habits is inaccurate—and it is. But this explanation is not applied consistently. It is never used against the studies mentioned in chapter 1, those that claimed a connection between fat intake and heart mortality in various countries, although the uncertainty in these studies was much higher. The researchers did not determine dietary information by any questionnaires or surveys at all, but instead on

estimates of the average intake of fat based on the highly uncertain assumption that people eat what is available. Such soft evidence should be treated with the utmost care but diet-heart supporters refuse to do more than applaud investigations that support their theories

But even information gathered through direct questioning is inaccurate. A crude relationship should appear if a sufficiently large number of individuals are meticulously questioned. If not, the influence of the diet, if any, must be so weak that it cannot possibly have any importance.

Diet-heart supporters also argue that most people in Western communities already eat great amounts of fat and cholesterol. This argument declares that we have already crossed a threshold of too much animal fat in the diet so that more fat does not make any impact on our blood cholesterol.

The argument is in conflict with the studies I have mentioned above. Dr. Nichols and his team, for instance, declared “*The distribution of daily intake of total fat, saturated fat, and cholesterol by the individuals in this study was quite broad.*” And indeed it was. For about 15 percent of the men less than 12.8 percent of the calories came from animal fat, and for about 15 percent of the men more than 20 percent of the calories came from animal fat.

Consider now that it is the goal of the *National Cholesterol Education Program* to lower the intake of animal fat of all Americans to about ten percent of their caloric intake. Almost 15 percent of the participants in the Tecumseh study already ate that amount of animal fat that low, and yet it was impossible to see a difference between the blood cholesterol of those who ate small amounts of animal fat and of those who ate much more. Does it make sense to recommend this drastic reduction of animal fat if the cholesterol of those who already eat that little is just as that of the epicure?

The Mayo Clinic study also revealed a wide range of fat intake. The lowest intake of animal fat was 15 grams per day (less than 10 percent of the caloric intake); the highest was 60 grams per day. In the Bogalusa study, the range was still broader. The lowest intake of *all* fats was 17 grams per day, the highest 325 grams per day. (No information was given about the relative proportion of animal fat to vegetable oils.)

In Jerusalem a team of researchers, led by Dr. Harold Kahn studied the diet and blood cholesterol of ten thousand male Israeli civil servants. The dietary habits varied considerably between people from Israel, Eastern Europe, Central Europe, Southern Europe, Asia and Africa. The intake of animal fat varied from ten grams up to two hundred grams daily, and there were also considerable differences between their cholesterol values.^[97]

If the intake of animal fat were of major importance for the cholesterol level in the blood it should be possible to find some kind of relationship from a study of so many individuals with such great variations in blood cholesterol and dietary habits. But there was no relation in this Israeli study either. Extremely low cholesterol values were seen both in those who ate small amounts of animal fat and in those who ate the most animal fat, and high cholesterol values were seen at all levels of animal fat intake.^[98]

The scientists from Israel also studied the value of various ways of dietary questioning. Many studies have recorded the diet during only one 24 hour period only. Even if this information were accurate it may not be representative of the diet for the rest of the year, far less for a whole life-time. The Israeli scientists found that the best information came from a questioning over several days and during different seasons of the year, the method used in the study of the bank tellers. Using this expensive and time-consuming method in a smaller study of sixty-two individuals they could not find a correlation either; the correlation coefficient between animal fat intake and blood cholesterol was zero point zero.

Vegetarians usually have lower cholesterol than other people and they eat little animal fat. But vegetarians differ from the rest of the human population in more than their diet. They are usually more interested in their health, they usually smoke less, they are usually thinner, and they usually exercise more often than other people. Whether it is their diet, or their other living habits, or perhaps something else that lowers their blood cholesterol is unknown.

The fact that blood cholesterol is influenced by the diet in laboratory experiments and clinical trials but not in people who live without the interference of scientists and dieticians has a simple explanation: Blood cholesterol is controlled by more powerful factors than the diet. If these factors are kept reasonably constant in a laboratory experiment or a clinical trial, it is possible to see the influence of the diet alone.

The question, however, is whether a lowering of blood cholesterol by diet is permanent. As mentioned above, the body tends to keep blood cholesterol at a fairly constant level. The dietary experiments mentioned above went on for a few months at most. The cholesterol control mechanisms of the human body probably needs more time to adapt to a fat intake that differs from the usual one. Over millions of years mammals, including homo sapiens (our kind of men), have developed effective mechanisms to counteract unfavorable changes in all blood constituents. Salt and water, for instance, are regulated rapidly within narrow limits, because even small deviations may have a strong influence on the functions of the body. Extreme variations of other substances, such as proteins and fats, have no serious consequences in the short run; the adaptation is thus slow. But in due time also these deviations may be counteracted; this has been demonstrated by the Masais, the Samburus, the Somalian shepherds, and many others.

Food and blood cholesterol

You may ask why I have written so much about fats. After all, it is blood cholesterol levels that matter, not the level of fats in the blood, and the most important thing should be how much cholesterol we eat, not how much fat. If we eat lots of cholesterol, doesn't our blood cholesterol increase? It is not that simple.

Have you limited your daily consumption of eggs, the richest source of cholesterol in our food? If so, the following statement will either make you angry or allow you to breathe a sigh of relief. The cholesterol in your food has little or no influence at all on the cholesterol in your blood.

Even the most zealous proponents of the diet-heart idea know this very well, but they keep silent, because how on earth can you promote the idea that high blood cholesterol is a threat while allowing people to eat as much cholesterol as they like? The truth is that cholesterol in your food can't influence your blood cholesterol by more than a few percent.

Numerous studies have shown that in people who eat a normal Western diet, the effect on blood cholesterol of eating two or three extra eggs per day over a long period of time can hardly be measured.[\[99\]](#)

To find out how eating eggs influenced my own cholesterol, I once used myself as a human guinea pig without asking for permission from the ethics committee. Before and during the experiment I analyzed my blood cholesterol. My cholesterol at the start of the experiment was 278 (7.13), close to a determination made ten years earlier. The results are shown in **Table 3B**.

Table 3B. Egg consumption and cholesterol values in one skeptical Swedish doctor.

| Day | Number of eggs consumed | Blood cholesterol (mg/dl) |
|-----|-------------------------|---------------------------|
| 0 | 1 | 278 mg/dl |
| 2 | 4 | - |
| 3 | 6 | - |
| 4 | 8 | 266 mg/dl |
| 5 | 8 | 264 mg/dl |
| 6 | 8 | 257 mg/dl |
| 7 | 8 | 274 mg/dl |
| 8 | 8 | 246 mg/dl |

The data from my daring experiment showed that instead of going up, my cholesterol went down a little, even though I was eating two or three times more cholesterol than my body normally produces itself. Why didn't my cholesterol go up?

Of course, one should be careful about drawing conclusions from an experiment on a single individual. However, it is not forbidden to speculate a little; after all, eight eggs a day represents a substantial amount of cholesterol.

Most probably, no change took place at all. Cholesterol measurements can never be as exact as measurements of your weight or height. If you take a blood sample, divide it between ten test tubes and analyze the cholesterol concentration of each tube, you will probably get ten different values. The difference between the lowest and the highest can be as great as 15 percent or more, although the true concentration is, of course, identical in all nine samples. Normal day-to-day cholesterol variations make it even more difficult to get an accurate

measurement. The small decline in my cholesterol level could simply have been due to imprecise measurements.

What we do know is that when we eat large amounts of cholesterol, our cells slow down their own production of this vital substance. Part of the surplus in the blood is temporarily stored in the liver and part is excreted with the bile. In my case, this regulation was performed so efficiently that my blood cholesterol did not rise, in spite of a substantial increase in my daily cholesterol intake. Perhaps my cholesterol would have finally gone up if I had continued longer with my experiment, but even if eggs are a good and nutritious food, who wants to eat eight eggs a day?

Non-responders

Proponents of the diet-heart idea would argue that I am what they call a “non-responder.” According to this view, some members of the human race are able to maintain the same blood cholesterol level even after having eaten large amounts of cholesterol. Maybe so, but in that case, most of mankind are non-responders. This can be deduced from a study performed by Dr. Martijn Katan and his group at the Agricultural University in De Dreijen, the Netherlands.[\[100\]](#) They gave test individuals a low-cholesterol diet for two weeks, followed by a high-cholesterol diet for another two weeks.

In some of the test individuals, called the hyper-responders, the cholesterol rose by 11 to 42 percent, whereas in others, called the hypo-responders, the cholesterol change varied from a *decrease* of 11 percent to an increase of 4 percent. These two groups, the hypo- and the hyper-responders, then participated in a second experiment, again with a high-cholesterol diet for two weeks. But this time their cholesterol levels changed very little, and the change was about the same in each group. Thus, the experiment did not support the idea about hypo and hyper-responders.

Surprised and disappointed with this unexpected result, the researchers decided to perform yet another experiment, this time with a total intake of almost one gram of cholesterol per day, and for three weeks instead of two. This time it was a little better, but there was a lot of individual variation. As the authors wrote: *“Quite a number of subjects who appeared hyper-responsive in one experiment proved to be hypo-responsive in another experiment.”*

To get a significant difference between the two groups, the researchers resorted to the so-called one-tailed t-test—a less stringent parameter that is not accepted among scientists for use in research where the expected result can go in either direction—and here the result certainly went in both directions. It is not particularly scientific either to continue an experiment until you get an outcome that suits your hypothesis, because sooner or later chance will produce a suitable result. The explanation for the haphazard results is, of course, that good friend of uncritical researchers, Mr. Chance.

Obviously, cholesterol in the diet has only a marginal influence on cholesterol in the blood. Why? Because we regulate our own production of cholesterol according to our needs. When we eat large amounts of cholesterol, our body’s production goes down; when we eat small amounts, it goes up.

But even if dietary saturated fat or cholesterol raises cholesterol in the blood a little, this effect is not particularly important—this is what scientists call a surrogate outcome. The crucial question is whether a high intake of saturated fat leads to cardiovascular disease, and whether you can prevent such disease by lowering the intake. In the next chapter you will see that both assumptions are false.

Myth 4: High Cholesterol Blocks Arteries

Theorists almost always become too fond of their own ideas, often simply by living with them for so long. It is difficult to believe that one's cherished theory, which really works rather nicely in some respects, may become completely false.

Francis Crick

Nobel Prize laureate together with James Watson for discovering the structure of DNA

Cholesterol: Villain or Innocent Bystander?

Although scientists should do more questioning, in cholesterol research one statement never gets questioned because it is considered just as self-evident as the law of gravity. Even many opponents of the diet-heart idea neglect to question this statement. And what is this statement? It is that, when its level is high in the blood, cholesterol passes through the vessel walls, transforming arteries from smooth canals to rocky rapids.

Doctors and scientists may debate whether cholesterol leaks in passively or is actively transported by cells. But there is a general agreement about the importance of the cholesterol level of the blood; the higher it is, the faster the arteries become sclerotic.

As early as 1953, Ancel Keys wrote: *"It is a fact that a major characteristic of the sclerotic artery is the presence of abnormal amounts of cholesterol in that artery. And he added: this cholesterol is derived from the blood."*[\[101\]](#)

No proofs, and no arguments, not from Keys and not from his followers. Cholesterol comes from the blood, and that's the end to it. Scientists discuss how high the cholesterol level has to be for atherosclerosis to start, but they do not discuss whether the cholesterol level by itself has any importance. The role played by cholesterol in the process of atherosclerosis is no longer under discussion; it has been settled forever, or so we are led to believe. Let us have a closer look at the facts.

Calcium and kidney stones

A finding that has convinced many scientists is the fact that when you inject cholesterol molecules made radioactive they are found at a later time in the atherosclerotic lesions. But calcium salts of kidney stones have been circulating in the blood also, once upon a time. It isn't possible, however, to prevent or eliminate kidney stones by lowering the calcium level in the blood, nor is it possible by lowering dietary calcium. And if we exclude a rare disease called hyperparathyroidism calcium stones are certainly not due to a high calcium level in the blood because the level in patients with kidney stones is not higher than normally. The calcium salts in kidney stones originate from the blood, but we simply do not know why and how they become organized in the kidneys as stones. *Any* substance in a pathological structure in our body has at some time been transported by the blood. Its presence in the structure, be it a kidney stone or a sclerotic plaque or anything else, doesn't necessarily mean that the structure is produced by a high level of this substance in the blood. That high blood cholesterol doesn't produce atherosclerosis is also evident from many studies.

If cholesterol molecules circulating in the blood tend to settle in the arterial wall and produce atherosclerosis only because the blood contains more of them than normal, then people with high blood cholesterol should on average be more sclerotic than people with low blood cholesterol, this is pure logic. The protagonists also claim that this is the case. Let me show that they are wrong.

False connections

There are many ways for scientists to find a false correlation, and false correlations can mislead both scientists and their readers. Good, sound science is difficult; false answers are all too easy, even for the scientist who means well.

Let us start with the situation where we have recorded the blood cholesterol and the degree of atherosclerosis in a large number of dead individuals. To see if blood cholesterol and degree of atherosclerosis are related we draw a diagram where blood cholesterol is read on the horizontal axis and the degree of atherosclerosis on the vertical axis. We may now obtain a false correlation if we have put together young and old individuals in our study, because in most studies old people on average have higher cholesterol and more atherosclerosis than have young people. Therefore, the young

individuals with their somewhat lower cholesterol and their low degree of atherosclerosis will mainly be represented by the symbols in the lower, left part of the diagram, and the old ones with their somewhat higher cholesterol and much more pronounced atherosclerosis will probably be represented by the symbols in the upper, right part. Thus, if we do not know the age of the studied individuals we may think that there is a correlation between blood cholesterol and atherosclerosis, when in fact it is between cholesterol and age, and between atherosclerosis and age.

It is therefore necessary to study narrow age groups. For a scientifically valid answer, the question to ask is whether someone of sixty who has high blood cholesterol is more sclerotic than another sixty-year-old person whose blood cholesterol is low.

A false correlation may also appear if the study includes many participants with familial hypercholesterolemia. Such people always have very high cholesterol values and some of them have severe atherosclerosis early in life. All of them will therefore be represented by symbols in the right side of the diagram; many of them in the upper corner. If many of these people are studied together with normal people, the statistics will be skewed and will automatically produce a correlation between cholesterol and atherosclerosis. And if the written results of the study present only the mean statistical values and correlation coefficients, or if the symbols do not specify the participants with familial hypercholesterolemia, readers will not be able to see this bias or skewing effect.

I shall not discuss here whether it is the high cholesterol that causes atherosclerosis in people with familial hypercholesterolemia or not. What is certain, though, is that these people have a rare, genetic abnormality in their ability to metabolize cholesterol. And, because of that, they cannot be used as proof that high cholesterol causes atherosclerosis in the 99% or more of the normal population. Individuals with familial hypercholesterolemia should be studied separately, not mixed in with normal people, that is elementary. Nevertheless, almost all studies include both groups and in many studies people with familial hypercholesterolemia are heavily overrepresented.

Thus, many factors can prevent a scientist from arriving at valid statistical calculations. Let's keep that fact in mind as we look at some of the scientific

studies that have convinced the scientific community that high cholesterol causes atherosclerosis.

Landé and Sperry

The first study of a possible correlation between blood cholesterol and degree of atherosclerosis was published by the pathologist Kurt Landé and the biochemist Warren Sperry at the Department of Forensic Medicine of New York University.[\[102\]](#) The year was 1936. To their surprise, they found absolutely no correlation between the amount of cholesterol in the blood and the degree of atherosclerosis in the arteries of a large group of individuals, who had died violently. In age group after age group their diagrams looked like the starry sky. Because Landé and Sperry were cautious and methodical, they should have wrecked the diet-heart idea before it ever began years later. Or, more accurately, if those who promoted the diet-heart idea had read Landé and Sperry's paper, they would probably have dropped the idea at once.

But the few who remember Landé and Sperry misquote them and claim that they *found* a connection,[\[103\]](#) or they ignore their results by arguing that cholesterol values in the dead are not identical with those in living people.

Veterans explained away

That problem was solved by Dr. J. C. Paterson from London, Canada and his team.[\[104\]](#) For many years they followed about 800 war veterans. These men were confined to a hospital because they were mentally ill or needed residential care. Over the years, Dr. Paterson and his coworkers regularly analyzed blood samples from the veterans. Because the veterans were all between the ages of sixty and seventy when they died, the scientists were informed about the cholesterol level over a large part of the time when atherosclerosis normally develops.

Blood cholesterol varied considerably from one veteran to another but for each individual it was fairly constant, so that, for example, those who had low cholesterol at the beginning of the study usually had low cholesterol just before they died.

A postmortem was performed on all the veterans who died. Changes in their degree of atherosclerosis were measured, and so was the amount of

cholesterol in the walls of the arteries. Like Drs. Landé and Sperry, Dr. Paterson and his colleagues did not find any connection between the degree of atherosclerosis and the blood cholesterol level; patients with low blood cholesterol were just as sclerotic as those with high blood cholesterol.

But the studies of the veterans were also explained away. Supporters of the diet-heart idea declared that the veterans had eaten the same food and that there are much greater variations in the amount of dietary fat consumed by people living outside an institution.

Although we don't know what each individual veteran ate, it is probably safe to assume that many supplemented the hospital diet with candy bars and potato chips and other supposedly unhealthy foods. It is probably a safe assumption, too, that some of the veterans left the fatter foods untouched on their plates in the dining hall, whereas others did not. But let us assume that all these men ate approximately the same amount of fat, confined as they were to an institution. In that case, the diet-heart idea that blood cholesterol depends on the amount and type of fat we eat must be wrong, because the blood cholesterol levels of these veterans varied considerably, just as much as in the study by Landé and Sperry.

High cholesterol and smooth arteries

In the city of Agra in India, Dr. K. S. Mathur and his coworkers have performed a similar study.[\[105\]](#) Their first step was to measure blood cholesterol in twenty patients shortly before death and then a varying number of hours afterwards. They found that the cholesterol values were nearly the same if sampled before death and within sixteen hours after. Thus, they showed that blood samples taken very shortly after death are reliable; an important confirmation of the study done by Drs. Landé and Sperry. Dr. Paterson's group in Canada did a similar test and with the same result.

Next, Dr. Mathur and his colleagues studied two hundred people who had died suddenly by accident without any preceding disease. Like Drs. Landé and Sperry, and like Dr. Paterson, the Indian researchers could find no connection between the level of cholesterol and the degree of atherosclerosis. Of the two hundred dead people, those with low blood

cholesterol had just as much atherosclerosis as those whose cholesterol was high.

Similar studies have also been performed in Poland[\[106\]](#), in Guatemala[\[107\]](#) and in the USA,[\[108\]](#) all with the same result: no correlation between the level of cholesterol in the blood and the amount of atherosclerosis in the vessels.

We are the only good ones

But some studies *did* find a correlation. One of them was the famous study from Framingham, Massachusetts. The correlation in Framingham was minimal, however. In statistical terms, the correlation coefficient there was only 0.36. Such a low coefficient indicates a desperately weak relationship between variables, in this case, of course, between cholesterol and atherosclerosis. Usually, scientists demand a much higher correlation coefficient before they conclude that there is a biologically important relationship between two variables. Usually, but Framingham was not quite the usual case; it involved huge amounts of government funding.

The very low correlation coefficient was arrived at after much study. First, many of the townspeople of Framingham had their cholesterol tested several times over a period of several years. Then, Dr. Manning Feinleib of the National Heart, Lung, and Blood Institute, led a team of coworkers in studying the coronary vessels of those who had died. The researchers were eager to learn which of the many factors they had studied was most important in the development of atherosclerosis in these dead people from Framingham. Was it blood cholesterol or the number of cigarettes smoked, or something else?[\[109\]](#)

After carefully describing the atherosclerosis in the coronary arteries of the dead people, Dr. Feinleib and his associates concluded that it was blood cholesterol levels that best predicted the degree of atherosclerosis. Neither age nor weight nor blood pressure nor any other factor was as good as blood cholesterol. But the correlation coefficient between cholesterol and atherosclerosis was a mere 0.36.

The written report of the study offered no diagrams and no information about cholesterol and atherosclerosis of each of the individuals whose

bodies had been examined. And the report did not discuss the very low correlation coefficient; it didn't even comment upon that matter.

When scientists reach a result contrary to all others, it is routine—not merely usual but routine—to provide a detailed report about the result and also to discuss any possible ways in which the study may have been biased away from accuracy and truth. In the Framingham case, there was an especially great need for this routine scientific procedure to be followed. Not only was the correlation coefficient so trivial, but this study, funded with millions of taxpayers' dollars by The National Institute of Health, could have a major impact on national health care and the American economy. If there was no connection between cholesterol and atherosclerosis, as all the previous studies had shown, then there was no reason to bother about cholesterol or the diet. And billions of taxpayers' dollars could have been spent more wisely than in lowering cholesterol of healthy people.

But the scientists conducting the Framingham study had no reservations. They were eager to stress their own excellence and to highlight the weaknesses of Dr. Paterson's study of Canadian war veterans. In their report, they did not mention the studies of Drs. Landé and Sperry at all, nor the study of Dr. Mathur in India, nor the studies in Poland or Guatemala and the USA. And when the Framingham study authors mentioned Dr. Paterson's study, it was only to criticize without putting their own cards on the table. Some of those hidden cards are fascinating to wonder about.

For example, how were the dead of Framingham chosen for postmortem examination? From 914 dead individuals the researchers examined only 281. And from the 281, they selected 127 (14 percent of all dead) who became the subjects of an autopsy program especially designed to investigate the heart and its vessels.

Thus, those chosen for autopsy in the Framingham study were not a random sampling of the population, as they had been in the previous studies. The report from Framingham said nothing about the selection criteria, although scientific studies routinely do. Usually the determining factor is age. A postmortem is seldom performed on people who have died peacefully in old age, as most of us will. Primarily, a postmortem is restricted to young and middle-aged people, who have died before their time, and so it was in the

Framingham study. Almost half of those autopsied were younger than 65 years. For this reason, the autopsied subjects must have included a relatively large number with familial hypercholesterolemia. Furthermore, people with this disease are of special interest to scientists studying the cholesterol problem and were probably chosen for autopsy in a program tailored to investigate coronary disease. With only 14% of the Framingham dead chosen for autopsy, the risk of preferably selecting those with this metabolic abnormality must have been great.

The ungrateful dead

Two studies with a design similar to that of the Framingham study have been published from Japan. One, led by Dr. Noriya Okumiya, took place at the Kyushu University;[\[110\]](#) the other, directed by Drs. Shuichi Hatano and Toshihisa Matsuzaki, occurred at the Geriatric Hospital in Tokyo.[\[111\]](#) In both studies the researchers said that the level of blood cholesterol correlated with the degree of atherosclerosis.

But in the first of these studies of dead Japanese citizens, the correlation appeared only in people with a low or normal cholesterol level; in the second, it appeared only in elderly people. The reports of the studies presented no individual figures, merely correlation coefficients, and these were as small as in the Framingham study. Moreover, the researchers did not explain the fact that the small correlation coefficient between cholesterol and atherosclerosis was present only in some groups but not in others.

More remarkably, among the dead people with high cholesterol, the degree of atherosclerosis was the same, whether these people were young or old. Logically, since atherosclerosis develops more and more as people grow old, it should develop faster in people whose cholesterol is high, or it should if the diet-heart idea were true.

Perhaps you're thinking that the degree of atherosclerosis was the same in all age groups because death had consistently weeded out only the most arteriosclerotic. But all degrees of atherosclerosis were present among those who had died.

The fact that atherosclerosis was just as severe in people of all ages with high cholesterol must mean that the cholesterol level was unimportant.

After all, if the cholesterol level had been of any importance, the old people should have been much more sclerotic than the younger ones, after living far longer with high cholesterol.

Similar peculiar results turned up in a study done in Oslo, Norway, where atherosclerotic diseases have been investigated for many years in a great number of the city's inhabitants. The project included a study of coronary atherosclerosis, led by Dr. Lars Solberg and his coworkers in cooperation with researchers at the Louisiana State University in New Orleans. The authors of the final report from this large study claimed that in Oslo, too, the degree of atherosclerosis correlated with the level of blood cholesterol. But, as in the previous studies, the correlation was very weak. And the correlation may have stemmed from the fact that the researchers did not consider the twenty-year age difference between the youngest and the oldest of the people whom they studied.[\[112\]](#)

In the investigation from Oslo, the weakness of the correlation between atherosclerosis and cholesterol appeared in many ways. For instance, many of the people who had no narrowings of the coronary vessels had cholesterol as high as in the people who had narrowings of all three coronary vessels. Furthermore, people with two narrowed coronary vessels had, on average, a lower cholesterol level than those with just one narrowed vessel. The scientific word for such results is *unsystematic*, which means that Mr. Chance and Mrs. Bias have determined their outcome.

Coronary angiography

If we take a solution of iodine atoms and inject them into a blood vessel of a living person, we can see, with X-rays, the inside of that vessel. This is the principle behind the medical technique called angiography. A narrow and flexible plastic tube is inserted into the femoral artery in the groin and pushed gently upwards through the aorta, the chief artery of the human body, until it reaches the vessel to be investigated; for instance those that provide the heart muscle with blood, the coronary vessels. When the tip of the catheter has been placed in the entrance of one of the coronary vessels, the iodine solution is slowly injected.

With the advent of bypass surgery that allow us to replace old and roughened coronary vessels with new and smooth ones, coronary

angiography has gained great importance. On the x-ray pictures, the shadows show how much the coronary vessels have been narrowed.

If we know the cholesterol values of the patients studied with coronary angiography and compare these values with the angiographic pictures we can test the cholesterol hypothesis. If blood cholesterol is the most important factor in the production of atherosclerosis, as we have been told for decades, then people with rough and irregular vessel shadows should have higher cholesterol than people with smooth artery shadows.

It seems as if every specialist in coronary angiography in America has performed his own study, funded with federal tax monies awarded by the National Heart, Lung and Blood Institute. In paper after paper published in various medical journals, using almost identical words, these medical specialists emphasize the importance of the blood cholesterol level for the development of atherosclerosis.[\[113\]](#)

But the reports offer no individual figures, only correlation coefficients, and these are never above a minimal 0.36, usually even smaller. And they never mention any of the previous studies that found no association.

Studies based on coronary angiography are fundamentally flawed, or they are if their findings are meant to be applied to the general population. Coronary angiographies are performed mainly on young and middle-aged patients with symptoms of heart disease, which means that a great number of patients with familial hypercholesterolemia must have been included in all angiographic studies. Again, there is an obvious risk for the kind of bias that I have described earlier.

The fact that this objection is justified was demonstrated in a Swedish study performed by Dr. Kim Cramér and his coworkers in Gothenburg, Sweden. As in most other angiographic studies the patients with the highest cholesterol values had on average the most sclerotic coronary vessels.

But if those who were treated with cholesterol-lowering drugs were excluded, and almost certainly this group must have included all patients with familial hypercholesterolemia, the correlation between blood cholesterol and degree of atherosclerosis disappeared.[\[114\]](#)

Another Japanese paradox

You have already heard that in Japan the food is meager, blood cholesterol is low and the risk of getting a heart attack is much smaller than in any other country. Given these facts you will most probably say that in Japan atherosclerosis must be rare.

The condition of the arteries of American and Japanese people was studied in the 1950s by Professors Ira Gore and A. E. Hirst at Harvard Medical School and Professor Yahei Koseki from Sapporo, Japan.[\[115\]](#) At that time US people on average had blood cholesterol of 220 mg/dl whereas Japanese had about 170 mg/dl.

The aorta, the main artery of the body, from 659 American and 260 Japanese people were studied after death. Meticulously all signs of atherosclerosis were recorded and graded. As expected atherosclerosis increased from age 40 and upward, both in Americans and in Japanese. Now to the shocking fact.

When the degree of atherosclerosis was compared in each age group there was hardly any difference between American and Japanese people. Between age forty and sixty Americans were a little more sclerotic than Japanese; between sixty and eighty there was practically no difference, and above eighty Japanese were a little more sclerotic than Americans.

A similar study was conducted by Dr JA Resch from Minneapolis and Dr's N. Okabe and K. Kimoto from Kyushu, Japan.[\[116\]](#) They studied the arteries of the brain in 1408 Japanese and in more than 5000 American people and found that in all age groups Japanese people were more sclerotic than Americans.

Those who want us to lower our cholesterol say that heart attacks are caused by atherosclerosis in the vessels of the heart, not in the vessels of the aorta or the vessels of the brain and they are right. Curiously, the coronary arteries of Japanese people are in fact less affected by atherosclerosis than the vessels of Americans and this may explain why Japanese people rarely get a heart attack.

But why are the aorta and the vessels of the brain just as sclerotic in Japan where cholesterol is much lower than in the US? If high cholesterol causes atherosclerosis in the vessel walls it should of course do it in any vessel because the cholesterol level is identical whether the blood comes from the

heart or the brain or any other organ. Isn't it much more likely that something else causes atherosclerosis than cholesterol? Something that may vary between the vessels, for instance the blood pressure? Blood pressure may vary greatly in various arteries depending on their. For instance, the tension of the coronary vessels, but not necessarily of other vessels, increases significantly when you are mentally stressed, and mental stress varies considerably between individuals and, as Dr. Marmot argued in his Japanese migrant study, probably also between populations.

Cholesterol is innocent

That people with a low cholesterol become just as sclerotic as people with a high cholesterol is, of course, devastating for the diet-heart idea. But the names of Landé and Sperry, Paterson, and Matur do not appear in the hundreds of papers and books published every year by the proponents of this idea.

“But what about the animal experiments?” the proponents of the diet-heart idea may ask. “You cannot explain away all the animal experiments!”

What the animal experiments have taught us is the subject of the next chapter.

Myth 5: Animal Studies Prove the Diet-Heart Idea

Rabbit tricks are positive successes.

Henry Houdini

Animals eat the wrong food

Perhaps you're finding the cholesterol question in man a little complicated and it is. But it's nothing compared to the situation in the animal kingdom, although, if it will comfort you, I'll say now that cholesterol studies just don't apply to man.

None of the mammals of the world are exactly like us as regards cholesterol. They have other amounts of it in their blood, they rarely eat as we do, and most of them do not become arteriosclerotic.

Many mammals never eat food containing cholesterol. If they are force-fed a cholesterol-rich diet, the cholesterol level of their blood rises to values many times higher than ever seen in normal human beings. And since such animals cannot dispose of the cholesterol they have eaten, every organ soaks up the cholesterol as a sponge soaks up water.

If animals are so different from us, how can we use them to prove that fat food and cholesterol are dangerous to human beings? Using cholesterol-rich fodder, it is possible to induce in rhesus monkeys arterial changes that vaguely resemble human arteriosclerosis, but it is not possible in baboons. How do we know if man reacts like a rhesus monkey or like a baboon or in some very different way?

These obvious weaknesses of animal studies have not prevented thousands of scientists from thinking up numerous ways to test animals in their laboratories.

There are however, many experiments and observations that may give us food for thought. Let's start by looking at arteriosclerosis and coronary disease in wild animals. What does arteriosclerosis look like in the arteries and heart of animals living outside the laboratories?

Arteriosclerosis with an appearance similar to that in man has been found in many animals, but more rarely and less widespread, probably because many

wild animals suffer a violent death as youngsters and thus rarely reach the age of arteriosclerosis. An animal with pronounced atherosclerosis may also be an easy pray.

Arteriosclerosis is found most often in birds, possibly because their blood pressure is higher than in land animals. But animal fat or cholesterol in the diet is not the cause. The seed- and grain-eating pigeons, for instance, and the fish-eating penguins become just as arteriosclerotic as the birds of prey.

There is no support for the diet-heart idea from the four-legged creatures, either. Arteriosclerosis has not been observed in beasts of prey, but it is not unusual in the vegetarian mammals that they devour. Also, sea lions and seals become arteriosclerotic; obviously it doesn't help them that their fish diet provides more polyunsaturated fat than most humans eat.[\[117\]](#)

Unfortunately, it is not this naturally occurring arteriosclerosis that has interested the students of cholesterol and coronary heart disease in animals. In a scientist with an open mind many relevant questions should arise. For instance, if vascular changes similar to human arteriosclerosis are found in some wild animals but not in others, why do these changes occur in the vegetarians and the sea animals and not in those feasting on animal fat? And is it possible to prevent or treat spontaneous arteriosclerosis in animals? Why have scientists studied the vascular changes created by force-feeding in laboratories and totally ignored the spontaneous arteriosclerosis?

Obviously, before they start their animal experiments, almost all scientists have concluded on their own that it is dietary fat and cholesterol that cause arteriosclerosis and coronary heart disease. So, instead of studying the animals' own arteriosclerosis they induce pathologic changes in the vessels by cholesterol-feeding and call it arteriosclerosis.

Let's have a look at some of their results.

Rabbits and cholesterol

The rabbit is a docile and placid animal. It doesn't bite, taking blood samples from its long ears is easy, and a rabbit is cheap. But the main reason that the rabbit has become the most common animal in the cholesterol laboratories is its way of reacting to cholesterol-rich fodder.

The rabbit, of course, is a vegetarian. If a rabbit is forced to eat food that it would never eat voluntarily and that it cannot digest or metabolize, its blood cholesterol rises to values 10-20 times higher than the highest values ever noted in human beings. Cholesterol percolates all through the rabbit; its liver and kidneys become fatty, its fur falls off, and its eyes become yellowish from a build-up of cholesterol that it can neither store, metabolize nor excrete. Finally, it dies, not from coronary disease but from loss of appetite and emaciation—it starves.

It is true that cholesterol is also deposited in the arteries of the rabbit, but nothing even remotely resembling human arteriosclerosis is seen. Cholesterol appears in different places in a rabbit's vessels than in man's, the microscopic changes are different, no haemorrhages or clefts appear as they do in man, no thrombus or aneurysms formation in the artery walls, and it is impossible to induce a heart attack by dietary means alone. The only effect that the rabbit shares with man is the increased cholesterol content of the arterial wall.

Overfeeding other beasts with cholesterol and animal fat produces varying results. The characteristics of the pathologic changes are similar to those in the rabbit, but the amount and location of cholesterol in the arterial walls vary. As a rule it is extremely difficult to provoke a heart attack in animals by dietary manipulations. To be successful, the scientist needs to combine diet with something else, such as a hormone injection or mechanical damage to the animal's arteries.

In rare experiments heart attacks have been seen in laboratory animals fed with cholesterol and animal fat. But this is no proof that the food is the cause, because both arteriosclerosis and coronary heart disease can also be seen in zoo animals fed their natural food. To prove that the unnatural food is causal, two groups of laboratory animals should be studied, with one group given the fat food and the other group given its natural food.[\[118\]](#)

Hunger-striking hearts

Those who experiment with animals often forget that the animals don't like it. This fact is crucial in studies of coronary heart disease, since frustrations and psychologic stress are considered a possible cause of the disease. In this context it may be interesting to look at some experiments performed by the

American physician and scientist Dr. Bruce Taylor and his coworkers. (This is the same Dr. Taylor whom I discussed in Chapter 2.) The diet-heart proponents often cite these experiments as proof that animal fat causes arteriosclerosis and coronary heart disease in man.

Dr. Taylor and his colleagues studied wild rhesus monkeys captured from the jungle. To produce “arteriosclerosis,” they gave the monkeys a fodder to which had been added a great amount of cholesterol. Throughout the experiment, the monkeys were housed individually in small dog cages, an arrangement they obviously disliked. To prevent escape the cages were reinforced with solid metal sheets.

The monkeys disliked their food perhaps more than their housing. They ate only a little and threw the rest around their cages. For long periods they went on hunger strikes.

Taking blood samples from these unhappy monkeys was difficult for all involved. To get enough blood, the groin artery of the monkey was punctured. Obviously this measure was unpleasant because at the sampling the monkeys resisted violently: they screamed, urinated and defecated.[\[119\]](#)

Of 27 monkeys, one had a heart attack after being experimented upon for four years in this basement laboratory in Chicago. Interestingly, this animal was hyperactive and extremely nervous, the scientists wrote.[\[120\]](#)

They didn't tell why it was interesting. Maybe factors other than the high blood cholesterol could have caused the heart attack in this intelligent animal isolated in a small cage for years, fed a bad-tasting diet and regularly subjected to terrifying blood samplings. Could that be? We don't know. Taylor and his colleagues, and most others who have cited their study in later papers, consider the cause to be the food and the high cholesterol level, that and nothing else.

In these experiments, the cholesterol of the monkeys climbed to values as high as ever measured in human beings. But it was not the cholesterol level that determined the outcome. This fact was demonstrated in an interesting experiment by Dr. Dieter Kramsch and his coworkers at the Evans Department of Clinical Research and the Cardiovascular Institute in Boston.

Dr. Kramsch and his colleagues studied as many monkeys as Dr. Taylor did, but Dr. Kramsch's project separated them into three groups. One group received fodder natural to monkeys, and the two others received fodder with added butter and cholesterol. The group fed the normal fodder and one of the groups fed the enriched fodder sat in their cages, inactive, throughout the experiment. The third group was allowed to exercise.

Only the inactive monkeys fed the butter and cholesterol developed coronary arteriosclerosis and coronary heart disease. But the monkeys that were allowed to exercise had wide, almost smooth coronary arteries, although their cholesterol was almost as high as that of the inactive monkeys![\[121\]](#)

Unfortunately Dr. Kramsch and his team did not report what happened with the inactive monkeys fed their normal fodder. This is most curious because had these monkeys not developed atherosclerosis, it would have meant that it is the combination of inactivity and high-fat food that produces atherosclerosis. And if these inactive monkeys on normal fodder had developed atherosclerosis just as did the inactive monkeys on high-fat fodder, it would have meant that inactivity, not high-fat food, is the culprit. Both alternatives would have added most interesting information. Could it be that the study results were so controversial that the researchers dared not report them? We don't know.

Honest proponents of the diet-heart idea admit that it is by experimenting on human beings, not on animals—to prevent arteriosclerosis and coronary heart disease, not to create them—that the idea may be proved. And they think they have successfully proved it.

In the next chapter we shall see if they are right.

Cholesterol lowering in children

Zealous proponents of the cholesterol hypothesis argue that we should begin cholesterol-lowering measures in childhood. They say that atherosclerosis starts in the early years; therefore, all parents should test their children's cholesterol and teach them to eat "properly," beginning at the age of two. This age limit was chosen because, in spite of their clever persuasions, diet-heart proponents would have difficulty convincing parents that whole milk, an allegedly poisonous food for adults, is harmful to babies. So "intervention" is held off until the tender age of 24 months, when most youngsters in the US are put on skimmed milk, milk substitutes and low-fat foods.

The argument for giving growing children a draconian diet can be made by claiming that the fatty streaks, the thin layer of cholesterol-laden cells situated on the inside of most arteries, are the forerunners of atherosclerosis. These fatty streaks appear even before we are born and are found in the vessels of all children, even in populations where atherosclerosis is rare. The public has not been told that the presence of fatty streaks does not mean that atherosclerosis will develop, and that there is no evidence that these fatty streaks are due to high cholesterol, or that they will disappear if we lower cholesterol in children.

In addition, high cholesterol in childhood does not mean that cholesterol will be high later in life. Several studies have shown that about half the children with high cholesterol at age two have normal cholesterol when they reach puberty.

And even if high cholesterol in childhood remained high in adulthood and predicted cardiovascular disease later in life, how should we treat the children? The answer from the proponents is: by diet! For this reason, many children are now being fed chemically processed margarine and a variety of processed, synthetic, low-fat products instead of nutritious and natural foods like whole milk, cheese, meat and eggs.

And the effect of diet on blood cholesterol is hardly measurable, especially in children. The only way to lower cholesterol effectively is by drugs—even the proponents admit that. But even if we had evidence that cholesterol-

lowering measures begun at the age of two were of benefit, we have no evidence that these measures would compensate for the side effects of an unhealthy diet or daily intake of drugs for many years because, luckily, such trials have never been carried out.

At best, emphasis on lowering cholesterol in children will create families of unhappy hypochondriacs obsessed with their diet and blood chemistry. At worst, it will have unfortunate effects on the growth of children because foods containing cholesterol and animal fats are rich in important nutrients.

Ravnskov U. Prevention of atherosclerosis in children. The Lancet 355, 69, 2000.

Myth 6: Lowering Your Cholesterol Will Lengthen your Life

But besides real diseases we are subject to many that are only imaginary, for which the physicians have invented imaginary cures; these have then several names, and so have the drugs that are proper for them.

Jonathan Swift (1667-1745)

Time for truth

As one scientific study after another has shown, people can gorge on animal fat for many years and still keep their blood cholesterol low. What we have learned also is that atherosclerosis and heart attacks may occur whether one's food is meager or fat, and most surprisingly, whether cholesterol is high or low. Given these facts, is there any reason to think that lowering blood cholesterol with diet or medicine can prevent heart attacks?

Based on what I have presented so far, the answer is no. In fairness, however, it still may be possible that high-fat food contains something other than cholesterol and saturated fatty acids that might be dangerous to the heart, or that high blood cholesterol slows the coronary circulation in some way other than by stimulating atherosclerosis. It might just be possible to reach the correct conclusion from the wrong premises.

The diet-heart idea itself is invalid, as I have already demonstrated in several ways. But the best way to know for sure if fat food and a high cholesterol level are dangerous is to use human beings as guinea pigs, to see if coronary heart disease can be induced by feeding these people animal fat or by elevating their blood cholesterol, or to see if heart attacks can be prevented by feeding the experimental subjects a low-fat diet or by lowering their blood cholesterol.

The idea to raise blood cholesterol during several years by dietary means is stillborn no matter how interesting it seems. The ethical committees that must approve all experiments on living creatures should certainly condemn the idea. Fortunately the Masais and other populations already have performed the experiment for us with well-known result.

It is much easier to get a permission to lower blood cholesterol. Many researchers have received permission and have tried although lowering blood cholesterol is possibly more dangerous than increasing it, as I shall soon explain.

To evaluate the effect of lowering blood cholesterol, all other risk factors must remain unchanged. If the test individuals also stop smoking, reduce their body weight or start

exercising, or receive treatment for their elevated blood pressure, change their work or get fired, fall in love or get divorced, move to another place with a different climate and culture, or do something else that may influence the condition of their heart or blood vessels, then we do not know what we should attribute the test result to. Is it the cholesterol lowering or is it something else? And this is not the only problem.

The diet-heart proponents say that the prevention of atherosclerosis cannot start too early in life. They add that the best results may be seen if prevention start before the rougher, more rocky deposits develop in our arteries. Here comes a problem, however, because coronary heart disease is uncommon before the age of fifty. To prove that cholesterol lowering prevents heart attacks in young and middle-aged people it is therefore necessary to study many thousands of individuals, preferably those at unusually high risk for heart attacks.

The question we ask is, if fewer heart attacks are seen among people whose cholesterol is lowered by treatment than among untreated people. A cholesterol lowering experiment must therefore include also untreated control subjects. By control subjects, we mean people who have identical risk factors for coronary heart disease, people with, on average, the same blood cholesterol, smoking habits, body weight, and so forth as the individuals who will be manipulated with treatment.

In sufficiently large studies, risk factors usually become evenly distributed by chance, provided that the test subjects and the control subjects are assigned to their two groups on the basis of some random feature such as their day of birth, or by leaving their assignment to a computer. Studies that include randomly selected control subjects are called controlled randomized studies.

As you can see, it is extremely difficult to design even the initial steps of a scientifically acceptable trial. The standards of science are high, however. In fact, they are so high that, even if we manage to select a test group and a control group with almost identical risks for heart disease, we must remember that almost identical and absolutely identical are not the same thing and that we will never know all the factors that may, or may not, stimulate the development of the disease in these people.

To these inevitable problems the trial directors themselves have added one more. If the test individuals are asked not only to lower their blood cholesterol but also to quit smoking, or to lose excess body weight, to get more exercise, or to do something else that we think may be beneficial, we do not know if a possible reduction of heart disease is caused by cholesterol lowering or by something else. Unfortunately, this method, called multiple risk factor intervention, has been used in many trials.

Sighted or blind?

Many researchers have tried to prevent coronary heart disease with diet or drugs. Some of the first trials had so many technical errors that even the diet-heart

proponents ignore them when they argue for their idea in their reviews.

One of the more serious errors was that the trials were not blinded. For a trial to be blinded, the patients must not know if they belong to the treatment group or to the control group. In the best experiments, called double-blind trials, not even the doctors know which group any given patient belongs to. Blindness prevents the treated subjects from feeling better merely because they know they are being treated and the control subjects from feeling worse merely because they know they are receiving no treatment; double blindness prevents the doctors who want the treated subjects to benefit, from leaping to conclusions based more on their own hopes than on scientific facts.

Up to 1968 the results of eleven dietary trials were known. Professor Jerome Cornfield at the University of Pittsburg and Dr. Sheila Mitchell at The National Heart, Lung and Blood Institute analyzed these trials. They found that the best results were seen if the doctors knew which group the participants belonged to. In six trials, the doctors knew, and in four of these six the number of heart attacks was reduced. In five trials, the doctors did not know, and in three of these five there was no difference between the number of new heart attacks in the control and treatment groups; in one of these five trials, even more heart attacks and more deaths occurred in the treatment group than in the control group.[\[122\]](#)

Unfortunately, many of the newer trials were neither single nor double-blind, as you will learn soon.

Soybeans against heart attacks

In the 1960s, in London, England, Professor Jeremy Morris led a team of physicians and scientists in an investigation to see if the use of soybean oil instead of animal fat could have some preventive effect on coronary heart disease. This oil is rich in polyunsaturated fatty acids, those that are considered protective against atherosclerosis and coronary heart disease. Enrolled in the trial were about four hundred middle-aged men who had previously been admitted to four London hospitals because of a heart attack; half of these were given a diet containing large amounts of soybean oil. (This is one of the few trials sponsored solely by a government, and not by a drug company or any other vested interest.)

The researchers could see no effect of the oil when the result was analyzed four years later. Although blood cholesterol had decreased considerably in the treatment group, fifteen had died of a heart attack. In the control group, fourteen had died; and the number of nonfatal heart attacks was identical for both groups.[\[123\]](#)

The authors of the report compared their result with a similar but unblinded experiment performed by Dr. Paul Leren, a Norwegian researcher from Oslo.[\[124\]](#) They concluded that, even if Dr. Leren had been more successful, the results of the

two trials taken together showed that it was not possible to prevent heart attacks by eating more polyunsaturated fat.

At about the same time, Dr. Seymor Dayton and his team from the University of California in Los Angeles conducted a similar trial.^[125] At a nursing home for war veterans they gave a treatment group of four hundred men a diet rich in soybean oil; the four hundred control subjects ate the institution's usual diet. Great efforts were made to prevent both patients and doctors from knowing who was treated and who was not.

Seven years later, a slightly smaller number of those who had eaten the soybean-oil diet had died from a heart attack. But the lower number of heart attack deaths was balanced by a higher number of cancer deaths.

Moreover, when the researchers analyzed the degree of atherosclerosis and the amount of cholesterol and fat in the arteries of the dead subjects, they discovered something peculiar. Although blood cholesterol had been lowered in the treatment group, there was no difference between the degree of atherosclerosis in the two groups. In fact, those who had eaten the diet laced with soybean-oil had even more cholesterol in the aorta, the chief artery of the arterial system, than those who had eaten the nursing home's standard fare.

The report from this well-performed trial did not explain why mortality from sclerotic vascular disease had decreased but atherosclerosis itself had not. The authors of the report concluded that the effect of the trial was impressive but that the trial alone was not enough to prove the diet-heart idea; it could not be used as an argument for recommending the diet for the entire population, since only old men had been studied and total mortality had not been lowered. The authors could also have said that the number of heavy smokers was much higher, indeed significantly higher according to the statistical tests, in the control group. Because smoking is considered a cause of coronary heart disease, the greater number of heart attacks in the control group could, logically, have resulted from smoking and not from diet.

The directors of the trials I have just referred to produced prudent reports about their efforts. It is difficult to find such balanced views from the directors of the trials that were to come.

The Coronary Drug Project

Blood cholesterol can be lowered in many ways. But which way is the most effective, and does it really help? These were the main questions when the American, government-supported National Heart, Lung and Blood Institute started the first mammoth trial to lower blood cholesterol. The year was 1967.

The trial, headed by professor Jeremiah Stamler from Chicago, was called *The Coronary Drug Project*. The drugs used were nicotinic acid, clofibrate (Atromidin®), thyroid hormone and estrogen (the female sex hormone), the latter given in two different dosages. Because these drugs and hormones lower blood cholesterol, they were considered appropriate for efforts to prevent coronary heart disease.

The subjects in The Coronary Drug Project were more than 8000 middle-aged men who had already had at least one heart attack. About 5500 of these men were randomly assigned to five treatment groups, with the rest assigned to a control group of roughly 2800. Altogether, 53 hospitals from all across the whole US contributed patients to this massive study.

The trial was well prepared. Anything of interest of coronary heart disease was studied by a large number of researchers. In the paper describing the project the list of researchers filled six pages.[\[126\]](#)

Within 18 months after the start of the trial, treatment for those who had received the high dosage of estrogen discontinued because the researchers found that the hormone was causing heart attacks instead of preventing them. And the patients were reluctant to take the estrogen because most of them became impotent and developed feminine-looking breasts. The investigators concluded, *“the potential value of this level of estrogen medication is probably limited.”*

Those who were treated with half dose estrogen continued the treatment,[\[127\]](#) but a few months later even the smaller dosage was found to be unfavorable. In addition to the side effects cited above, there were also more new cases of cancer.[\[128\]](#)

Treatment with thyroid hormone was discontinued, as well. Although blood cholesterol was lowered, the treatment seemed to induce heart attacks instead of decreasing them, just as was the case with estrogen.[\[129\]](#) The remaining groups continued to the end of the trial.

The result after seven years was depressing. Those who were treated with clofibrate had died just as often as those in the control group and many of them had had serious side effects of the treatment.[\[130\]](#)

Even more side effects were seen after treatment with nicotinic acid. Almost all complained of flushing or skin rashes, half itched, and one in five complained of stomach pains, nausea or other symptoms pertaining to the stomach and bowels. Other common side effects of nicotinic acid were gout (a painful inflammatory disease of the joints), burning pains while urinating, excessive sweating, serious disturbances of the heart rhythm, and various skin diseases.[\[131\]](#) As the directors of the experiment wrote in their report: *“Great care and caution must be exercised if this drug (nicotinic acid) is to be used for treatment of persons with coronary heart disease.”*

What they left unsaid, though, was how to exercise care and caution. And how can we? How are we doctors to know, before treatment begins, who will experience side effects? The drug was ineffective, anyway, to prevent fatal heart attacks. And why should we use an ineffective drug?

Nicotinic acid is still used today for prevention of coronary heart disease because of a peculiarity that appeared in a study years after The Coronary Drug Project ended.[\[132\]](#) Eight to nine years after all the treatment subjects stopped taking nicotinic acid, a follow-up study showed that fewer in the previously treated group had died from heart attacks and that fewer had died of any cause.

This result—no benefits from the drug during the trial, but fewer deaths years later—stimulated many speculations. One was that perhaps the nasty side effects had concealed its positive effects during the trial. The suggestion here was that perhaps it took many years before a lowering of blood cholesterol would show positive results. The books should be reopened after other trials also.

But clofibrate had lowered blood cholesterol just as much as nicotinic acid had during the trial. Yet clofibrate had prevented no deaths after many years. In fact, as the years passed, the number of fatal heart attacks in the group that had once received this drug was a little greater than in the control group. And nobody mentioned the follow-up findings of another large experiment, the WHO trial (see later). There, *more* people had died from heart attacks 4-5 years after their treatment with clofibrate ended.

It seems strange also, that a drug could help years after being discontinued, as strange as if the aspirin unsuccessfully taken to relieve a headache on Monday could prevent a headache on Friday.

It is hard to follow the logic in the conclusions from the cholesterol-lowering trials. Sometimes cholesterol lowering results in fewer deaths from heart attacks; sometimes the same degree of lowering results in more deaths. Sometimes the benefit is seen after a short time, sometimes not until years after trial's end. Or, if there is no benefit—the most common result—the trial directors declare that if the trial had continued longer, there might have been some benefit. However, when trials are sometimes beneficial and sometimes not, the more likely conclusion is that they aren't effective at all which means that their outcome depends on chance.

Primary versus secondary

The trials I have discussed so far are examples of secondary prevention. “Secondary” means that a disease—coronary heart disease in this instance—has already occurred, and that treatment is aimed at halting further spread of the disease. In contrast, a treatment aimed at preventing the disease in apparently healthy people is called primary.

There is a fundamental difference between primary and secondary prevention. Very often, people who have already had a heart attack are badly frightened and ask themselves, "Will I survive another coronary?" To prevent another heart attack, many are willing to submit to rather unpleasant kinds of treatment. Healthy people whose only defect is high cholesterol are less inclined to exercise, to renounce cigarettes and good food, and, on top of this, to take expensive drugs with unpleasant side effects. Healthy people thus make less compliant treatment subjects in a trial.

In addition, to achieve a significant result, a primary trial requires many more subjects, because the risk of a heart attack is considerably smaller for people who have never had a heart attack than for those who already have suffered one. While the subjects needed for a secondary preventive trial number in the hundreds, those needed for a primary preventive trial are many thousand. And if it is not possible to prevent a heart attack in those who have already had one, it is obviously more difficult to do so in healthy individuals. The results of the primary preventive trials have not been any more successful than those of the secondary preventive trials, even if the diet-heart proponents say otherwise. But now it is up to you, the reader, to judge for yourself.

The Upjohn trial

In the early 1970s, Dr. Albert Dorr and his coworkers at the Upjohn Company, a large pharmaceutical manufacturer in Kalamazoo, Michigan, started a trial to test Upjohn's new cholesterol-lowering drug colestipol (Lestid®).

At a large number of hospitals in the USA more than 2000 men and women with high cholesterol were selected. After the selection the local doctors consulted the directors of the Upjohn trial. In the offices at Upjohn, after being informed about certain laboratory values of the participants, the directors of the new trial decided which patients would have the drug and which would receive an ineffective sugar pill, the placebo.

To assign participants of a trial in this way obviously may introduce a bias, especially when those who assign them have vested interests. As you will see from the following the distribution of risk factors in the treatment and control groups became far from even.

Two years later the result was analyzed. No effect was seen for the women in the trial. But the effect for the men was amazing. After only two years, the number of heart attacks had been halved for the men in the treatment group. Such remarkable results have never been achieved in any trial before or since.[\[133\]](#)

There was a snag, however. In the control group, the number of individuals with familial hypercholesterolemia was greater than in the treatment group. As the prognosis for these people is worse than for others; some of them die young from heart attacks and lack of balance on this matter may well have biased Upjohn's result.

The WHO Trial

At the same time a similar trial was being performed under the auspices of the WHO. This trial, led by Professor Michael Oliver at the University of Edinburgh, Scotland, used clofibrate, the same drug that was used in the Coronary Drug Project.

For the WHO trial, blood cholesterol was analyzed in 30,000 healthy, middle-aged men in Edinburgh, Prague, and Budapest. The men with the highest blood cholesterol were selected for the treatment, a total of ten thousand individuals. Half of them were treated with clofibrate, the other half with an ineffective placebo.

After about five years treatment, 174 of those who had been taking the placebo had suffered a non-fatal heart attack, but only 131 of those treated with clofibrate. Apparently the drug was a success.

But the number who had *died* from heart attacks was equal. Worse yet, considerably more of those who had been treated with the drug had died from other diseases. In all three cities more men had died in the treatment group. Taken together, 128 died in the clofibrate group, 87 in the placebo group. And 4-5 years after the trial, even the number who had died from heart attacks was larger in the treatment group.[\[134\]](#)

Clofibrate is still recommended as a useful drug in many countries, however.

Fat food and fit Finns

One of the nations with the highest mortality from coronary heart disease is Finland. The mortality is especially high in the province of North Karelia, for reasons that no one knows. The coronary mortality rate increased year by year up to the 1960s. Of course the Finnish health authorities were concerned. To them, it was self-evident that the cause was high cholesterol, because in Finland it is higher than anywhere else, and some of the highest values are found in North Karelia.

A team of doctors and scientists at the university in Kuopio headed by Professor Pekka Puska decided to do something about the problem. They chose to start in North Karelia. To see if their efforts were beneficial, they used the district of Kuopio as their control, because people in Kuopio died just as often from heart attacks as the people of North Karelia did and their cholesterol was equally high.

In 1972, a public health campaign began throughout North Karelia. Its aim was to prevent heart disease by focusing on smoking, fat food, and high blood pressure. In the mass media, on posters, at public meetings, and through campaigns in schools and work places, the message was proclaimed. In Kuopio nothing was done; here, people were allowed to live as they had traditionally lived.

Five years later the number of heart attacks among North Karelian men had decreased from 0.77 to 0.63 percent each year. The total mortality had also decreased. Possibly

this trend could improve in the future, the leaders of the campaign wrote in their report.[\[135\]](#)

There was a problem, however. In Kuopio, where the citizens served as control subjects, the number of heart attacks had decreased even more, among women as well as men, although the townspeople ate and smoked as they had before. In fact, heart mortality had decreased in all the provinces of Finland (figure 6a).

The disappointment of the campaign leaders is easy to imagine. All this enthusiasm and all this work were of no use. On the other hand, negative results can be and are interesting for those whose curiosity is intact and who are more interested in knowledge than in the defense of old positions.

Two conclusions may be drawn from the results of the campaign. First, it could not have been fat food or smoking or high blood pressure that caused the many heart attacks in North Karelia. If it were, the number of heart attacks should have decreased more in North Karelia than in the untreated Kuopio. Second, something had happened in the whole country to cause coronary heart disease to decrease, and it was not an improved diet, it was not reduced smoking and it was not a greater attention to blood pressure.

Unfortunately, the Finnish campaign team did not understand that they had found a track worth examining more closer. Instead, they published further papers with more analyses of their results.[\[136\]](#) More had died in North Karelia during the campaign than in Kuopio, they agreed, but in North Karelia there had been a greater reduction in the number of heart attacks than in all other areas of Finland. They also thought that the small irregularities of the mortality curve for North Karelia proved that their campaign had been of benefit.

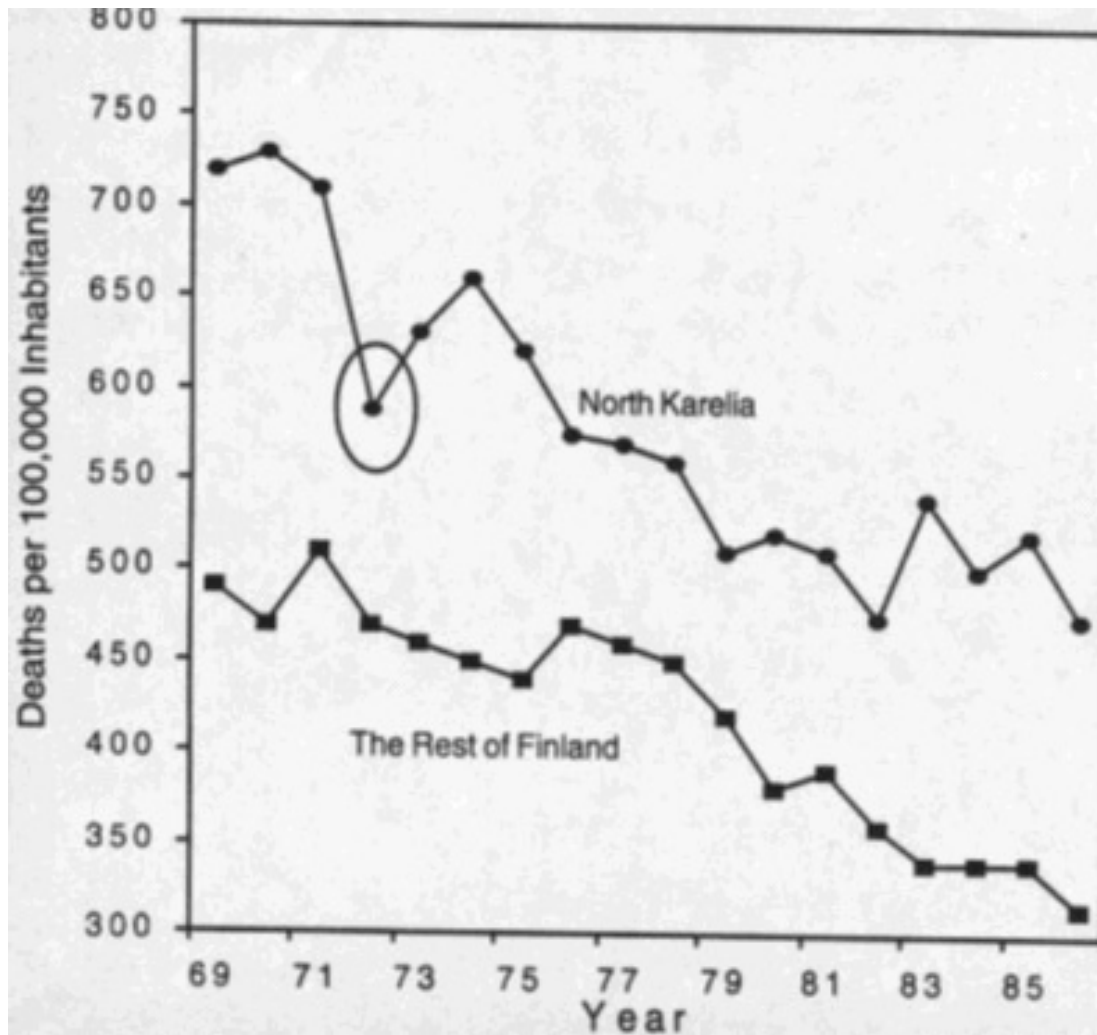


Figure 6a. Number of coronary deaths in North Karelia and in the rest of Finland.

The circle indicates the starting point of the North Karelia project. Observe that more died from heart attacks during the first three years of the project than during the year before the start, most probably a result of chance. Seen over a longer period of time, heart mortality had declined in North Karelia as well as in all of Finland and in many other countries. This decline had already started before the start of the North Karelia project. After Puska.

But what they did not mention was that the decrease in heart mortality had started several years before the start of the campaign, and that an examination of the curve over a longer period of time clearly revealed that the campaign had made no impact. In fact, if the small irregularities in the curve had any significance at all, heart mortality had *increased* during the first two years of the campaign. However, the investigators were so convinced of their success that they started similar campaigns in other parts of Finland.

One of the campaign leaders, Dr. Jukka Salonen, had a differing opinion. In a letter to the famous medical journal *The Lancet* he explained that, although he was a co-author of the North Karelia report, he had not been able to read the optimistic paper before its publication. He did not think it possible to draw the conclusions presented in the paper and admitted that the steeper slope of the mortality curve for North Karelia could be explained in a variety of ways. For instance, he wrote, the increased heart disease seen during the previous decades had come later to North Karelia; the decrease, therefore, had come later, too. The critical factor, however, was whether the campaign had changed the trend in North Karelia (which it had not). Dr. Salonen wrote that the North Karelia project could not be used as evidence to say that the risk factors either caused or did not cause heart disease; the project had merely shown that intervention is possible and can lead to a change in risk factors.^[137]

But, as Professor Michael Oliver of Edinburgh, answered: “*What was the aim of trying to change risk factors unless they were thought to have some causative role and unless positive results were expected?*”^[138]

Valio

On June 23, 1988, there appeared a full-page advertisement in a great many Finnish newspapers. The ad had been paid for by Valio, a large farm cooperative that markets about 90 percent of all milk products in Finland. It presented “*five facts about dietary fat you have wished to hear about but nobody has told you.*”

The five facts were as follows.

1. In Finland people eat less fat than in many Western European nations.
2. There is no direct connection between a nation's intake of animal fat and its mortality from coronary heart disease.
3. Fat intake and mortality from coronary heart disease have changed in opposite directions in many countries.
4. Mortality from coronary heart disease has decreased in Finland, despite the fact that the Finnish people has increased its consumption of animal fat.
5. Finally, a short summary of the North Karelia campaign was given.

It would be an understatement to say that the director of Valio's research department, Kari Salminen, met stormy weather; a hurricane is more like it. He was attacked in all Finnish newspapers and journals; almost every day during that summer and autumn, critical editorials, articles, and letters appeared in the Finnish press. No one could point to anything incorrect in the advertisement. Rather, it was the morality of the corporation that was rotten. The advertisement was condemned as partial, misleading,

and unethical; the claim was that Valio had selected convenient statistics for a deliberate manipulation of scientific data.

As director of the North Karelia project Pekka Puska was particularly offended. He thought that the various efforts of the campaign had produced marked effects at the start (correct, but effects in the wrong direction). The connection between dietary animal fat and heart disease has been better proved than most subjects in medicine, he wrote. The facts in the advertisement, he declared, did not tell the whole truth.^[139]

Kari Salminen, Valio's research director, answered that his company had merely done what the nutrition scientists had been doing for decades. Further, he replied, the advertisement had been designed as an invitation to debate and did not pretend to represent the whole truth.

The invitation was ignored. Debate was replaced by execution, and for many years Pekka Puska appeared in Finnish advertisements for margarine.

The Oslo trial

In Oslo, Norway, Dr. Ingvar Hjermann and his team thought that smoking and a high cholesterol level were the two most important causes of coronary heart disease and they wondered what would happen if smoking was stopped and blood cholesterol was lowered with an appropriate diet. To this end they studied about 1200 middle-aged men, mostly smokers, with high cholesterol. Half of these men received dietary advice and were encouraged to quit smoking. The other half received no treatment.

The result after five years appeared promising.^[140] In the group given dietary and smoking advice, 19 died from a heart attack. In the control group, the number was 35; if to the latter group was added a further control participant who had died suddenly of an unknown cause, the difference between the treatment and control groups became statistically significant.

A promising result for the diet-heart supporters. But does the experiment really prove that a faulty diet causes coronary heart disease?

In their paper, the Norwegian researchers pointed to two types of intervention, diet and cessation of smoking. They admitted that if dietary advice had been the only treatment their result would not have been sufficient as evidence.

In fact they had used three types of intervention, because subjects in the treatment group were also advised to reduce their weight. Evidently, this advice was followed: at the end of the trial, the mean weight difference between the two groups was almost seven kilograms (about 15 pounds).^[141] Opinions vary as to the importance of a 6-7 kilogram weight difference. It is evident that the risk of diabetes and high blood pressure is greater for overweight people, and diabetes and high blood pressure

predispose for coronary heart disease. Most proponents of the diet-heart idea also recognize overweight as a problem in heart disease. Wrote Dr. William Kannel, director of the Framingham project: “Avoidance and correction of obesity deserve a high priority among measures taken to avoid coronary heart disease, since the combined effect of the risk factors it promotes on coronary heart disease incidence is formidable.”[142]

Now to the crucial question. Which of the measures had had the decisive effect in the Oslo trial? Was it lowering of cholesterol by diet, was it the reduction of smoking, or was it the weight loss? Nobody knows.

Possibly you're asking, “Why didn't the Oslo trial leaders concentrate on the diet alone?” The answer to that question lies in a previous paper.

About ten years earlier, the researcher who had performed the Norwegian soybean trial, Dr. Paul Leren, had published the latest results of that trial. Although the number of heart attacks was reduced a little, Dr. Morris and his colleagues in England, using a similar treatment, had failed.[143]

But Dr. Leren analysed his own result and found that it might have been a good idea to change more than one risk factor, an approach called *multiple risk factor intervention*. Diet alone was unsuccessful.

Few of the diet-heart supporters rely on diet only in their trials; diet is often combined with other measures. When the LRC trial was being planned, the scientists stated frankly that diet alone was not enough, that to lower cholesterol drugs were necessary. [144]

It is laudable to try to prevent disease and premature death as effectively as possible. If all the measures are proved to be beneficial the frontier should of course be broadened. But in that case it is not possible to judge the influence of each measure individually. As no one has proved that diet alone is efficient it had perhaps been wiser to exclude the dietary advices, or to study them alone.

MR.FIT—Much ado about nothing

For many years scientists at the National Heart, Lung and Blood Institute had discussed how to prevent heart attacks. But before telling the American public what to do they needed solid proof that their advice would work.

They had rejected the idea of using diet alone. To be successful, they said, it was necessary to attack at least three of the major risk factors: high cholesterol, smoking, and elevated blood pressure. To this end the institute started a gigantic trial called the *Multiple Risk Factor Intervention Trial*—MR.FIT for short.[145] At its head was once again professor Stamler from Chicago.

The first step was to recruit more than 360,000 middle aged men from eighteen American cities. After a routine investigation the researchers selected about 12,000 men, namely those who were considered especially prone to get a heart attack.

The trial had every chance of succeeding. The test subjects had entered the trial voluntarily and they knew that their condition was considered dangerous. Although they felt hale and hearty (and, by normal standards they *were* healthy), they were overweight, their blood pressure was too high, and according to the experimenters their cholesterol scores hinted at premature death from heart disease. After the initial analyses, the men took part “with remarkably enthusiastic response.”

However, one of those initial analyses should have stopped the whole MR.FIT trial.

A decade before, a smaller, careful test study had been done. A comparison of the food eaten by the men in that study with the food consumed by the men selected for MR.FIT revealed that the MR.FIT participants had eaten more “healthfully” in all respects, more in accord with the diet-heart idea.[\[146\]](#)

Yet the blood cholesterol of the MR.FIT participants was higher!

Furthermore, initial surveys indicated that those MR.FIT participants who ate less saturated fat and cholesterol tended to have higher blood cholesterol! It was not exactly an encouraging finding for researchers who hoped to lower blood cholesterol by lowering just those components in the diet. But the directors of the trial responded only by declaring that, first, the odd evidence showed that cholesterol and saturated fat should be reduced more than originally planned for the MR.FIT treatment group. Second, they speculated that the fact that blood cholesterol was highest among the MR.FIT subjects who ate the most prudent diet showed that these men must have changed their diet at the last minute, right before the trial began.

Perhaps the directors were correct. The participants could have made eleventh-hour dietary changes in the days just before they were questioned about what they ate. But presented with experimental results contrary to what they have expected, scientists usually want to know “What's going on here? And why?” In accord with the long tradition of scientific inquiry, most scientist would have asked the MR.FIT participants if they really had shifted to a new diet right before the trial began. More than one hundred million dollars of taxpayers’ money could have been saved if some scientists had asked. If MR.FIT participants were eating as they had always eaten, even just before the trial, they would have demonstrated that diet is unimportant for the blood cholesterol level, and this enormously costly trial could have been cancelled then and there.

But no one asked. Or did they? Perhaps it would have been too heroic for the directors to cancel a trial with all these doctors, nurses, dieticians and, not least, the trial directors themselves, lined up and assured that they would have lucrative and

prestigious jobs for the next several years? If anyone asked, they didn't do it in public, and the trial continued.

The subjects were randomly assigned to two groups of equal size. Those placed in the treatment group and their families met in small groups to learn about the rationale behind the trial, and then to learn how to read food labels, to cook with minimal fat, and to change old recipes to meet new guidelines. In special sessions, the treatment subjects met for an intensive anti-smoking campaign; in selected cases, even hypnosis was used to help participants quit smoking. When necessary, individual counseling was provided by doctors, nutritionists, psychologists, nurses and other health professionals. Every four months, the treatment subjects were called in for blood sampling and to hear if they had fully understood all the new guidelines.

The dietary advice was, of course, aimed at reducing the men's intake of cholesterol and saturated fat and increasing their intake of polyunsaturated fat. High blood pressure was treated energetically, and subjects with weight problems were taught how to reduce calories and get more exercise. Dietician checked yearly to make sure that the men were really eating as prescribed.

The men in the control group received no advice, but they visited the center once a year for blood sampling and a questionnaire about their eating habits, and the results of these investigations were sent to their own doctors.

After seven years of treatment the effect was analyzed. The trial directors were satisfied that there had been major risk-factor changes. Blood pressure had been lowered considerably and many of the men had quit smoking.

But blood cholesterol had decreased by only seven percent. It had decreased in the control group, too, although the control subjects had scarcely changed their diet at all, so the difference between the two groups was only two percent.

Other risk factors had changed in the control group, as well. The one difference between the groups worth mentioning was that more of the control subjects continued to smoke.

The difference in number of deaths was small, too. In the treatment group 115 had died of coronary heart disease, in the control group 124. According to statistical precepts, such a difference could well have been due to chance. There was no statistical difference, either, in the number of deaths from all causes: 265 in the treatment group, 260 in the control group.^[147]

Customarily, when a scientific experiment does not produce results supporting a hypothesis the scientists admit it straight out. But this was not an ordinary experiment. More than a decade of hard work and several hundred millions of dollars had been invested in this most ambitious medical study to date. Hundreds of doctors, professors,

statisticians, dieticians, psychologists and others had been engaged. More than fifty scientific reports, most of them mammoth, had been published. And thousands of apparently healthy men, and their families, had been persuaded to take part in time-consuming investigations and to change their diet and way of life for many years. This huge effort could not possibly have been in vain.

And what had been preached for years to the American public about risk factors and heart attacks could not possibly have been wrong.

With a little statistical manipulation, the trial directors improved their results.

The participants were divided into smaller groups. Excluding from the treatment group a sub-group who did especially bad made the overall result appear better. Almost all the other sub-groups had had fewer fatal heart attacks. No great differences, and not all sub-groups, but almost all.

The trial directors concluded that the MR.FIT intervention program might have had a favorable effect for most of the participants. If some of the men had more heart attacks, it was because of the drugs used to lower blood pressure (although in another subgroup treated with such drugs, the outcome was better). It was also obvious that the outcome was favorable for those who had quit smoking, the directors wrote. In fact, the smoking habits explained the whole difference.

Within four years after the end of Mr.FIT, a total of 202 men in the treatment group and 226 in the control group had died from heart disease; again a difference that could be explained by chance (or by the smoking habits). But the investigators claimed that the figures proved the benefit of lowering blood cholesterol.[\[148\]](#)

More prudent diet-heart supporters admit that MR.FIT was a failure, but they usually add that the failure occurred because a two percentage lowering of blood cholesterol is too small to have any effect.

This is a reasonable objection, but with this objection diet is declared worthless as a preventive measure, because the diet had been changed as was aimed. The subjects in the treatment group had almost halved their intake of cholesterol, they had lowered their intake of saturated fat by more than 25 percent, and they had eaten 33 percent more polyunsaturated fat. In the control group the diet was practically unchanged.
[\[149\]](#)

If a scientific trial with almost unlimited economic and personal resources cannot lower cholesterol more than two percent over seven years, how is the over-worked general practitioner to succeed with a crammed waiting room and with no dieticians, or experts in behavior modification to hold his hand? And how is the patient to be motivated if he is not rewarded for all his trouble?

MR.FIT demonstrated that it is a good idea to quit smoking. But we already knew that, and most people can manage to quit without such costly help from society.

The final proof

Diet-heart proponents think that if we had a drug that could lower blood cholesterol sufficiently without any serious side effects, we could prevent or at least delay all diseases caused by atherosclerosis.

Here is a dream for all doctors. All that's necessary is a prescription pad and a gadget for measuring cholesterol. No time-consuming fuss with diet-counseling.

It is a dream, also, for the drug producers. A life-long lowering of cholesterol with expensive drugs in a substantial part of the population is far more profitable than for instance a brief treatment with cheap penicillin. In the offices of the drug manufacturers, the dream calculations are in the billions of dollars.

Large trials using clofibrate had not been especially encouraging, you may say. But other drugs seemed more promising. One of them was cholestyramine (Questran®).

The MR.FIT trial had excluded men with extreme cholesterol values (above 350 mg/dl), as it is considered unethical to place such “patients” in a control group without treatment. In the new jumbo trial^[150] called *The Lipid Research Clinic Coronary Primary Prevention Trial* (LRC), which would use the drug cholestyramine, all individuals with high cholesterol were included. The higher cholesterol, the better.

To solve the ethical dilemma, dietary advice was given in both the LRC's treatment and control groups. Although this advice would diminish the difference in outcome between the two groups, the degree of cholesterol lowering from diet was expected to be insignificant! The great difference would be created by cholestyramine.

To find about 4000 test individuals, blood cholesterol was determined in almost half a million middle-aged men. Never in history had so many people with such high blood cholesterol levels been involved in a medical experiment. In MR.FIT the upper three percent of the cholesterol range were selected, but men with the highest values were excluded. Here in LRC, only the upper 0.8 percent participated, without exception. Consequently, the mean blood cholesterol before the dietary treatment started was about 40 mg/dl higher than in MR.FIT meaning that most of the participants must have had familial hypercholesterolemia.

All LRC participants were investigated thoroughly, as in MR.FIT. After a few weeks dietary treatment, half of the men were started on cholestyramine medication, the other half on a supposedly inactive placebo powder.

Seven to eight years later, the results were analyzed. Although blood cholesterol in the treatment group had decreased by more than eight percent, the differences in the

numbers of heart attacks were so small that only chance could explain them. Of those who had taken cholestyramine, ten percent, or 190 men, had experienced a non-fatal heart attack, as against 11.1 percent, or 212, of the controls, a difference of 1.1 percentage points. As for fatal heart attacks, the figures were 1.7 and 2.3 percent, a difference of 0.6 percentage points, or twelve individuals.

But in the summary of the paper the result was given in another way. The lowering of non-fatal coronary heart attacks was said to be 19 percent and of fatal heart attacks 30 percent. These figures were arrived at by relating the percentage in the treatment group to the percentage in the control group, without any reference to the total number of men involved.

Even the exaggerated figures of the LRC report were a little too optimistic. To reach their 30 percent figure, the LRC directors included the uncertain cases, those who may or may not have died from a heart attack. But to reach their 19 percent figure, they excluded the uncertain cases. If it had been the other way around, the results would have been 24 percent rather than 30, and 15 rather than 19. In other words, they selected the most convenient figures.

Even worse, the LRC directors had lowered their own statistical demands. In a preliminary report[\[151\]](#) written several years before the trial ended, they had stated that, to be convincing, they would accept nothing less than the strongest statistical proof of their findings. In this case, it was a statistical level of 0.01, meaning that the trial results would be 99 percent accurate; and to ensure statistical accuracy, the researchers would use the very demanding two-tailed t-test.

Thus, the directors of the trial had begun by embracing the highest standards. Then, after the fact, when it was clear that the result of the trial did not measure up to their hopes, they shifted their demand for accuracy from 0.01 to the less stringent 0.05, and to the easy one-tailed t-test.

After their results were published, the LRC directors were severely criticized for their lowering of standards. But in response to critical letters to *The Journal of the American Medical Association*, they simply denied that they had ever declared in writing the high standards that they had originally aimed at. “*The term ‘significant’ was not defined in terms of a particular statistical probability level.*”[\[152\]](#)

Diet-heart supporters look offended if you tell them that, of half a million men, twelve were rescued from death. In fact, the number rescued was even smaller. Fewer in the treatment group died from heart attacks (32 against 44), but more died by violence or suicide (11 against 4). If we calculate in the ingenious way used by the LRC leaders and other diet-heart proponents, using relative risk and not absolute rate, the excess of violent deaths was huge; after all, eleven is 175 percent greater than four.

Hyping the benefit, minimizing the risks

If all men in the USA with blood cholesterol as high as in the LRC study received the same treatment and got the same result, two hundred lives would be saved per year, provided that the LRC result was not merely due to chance. However, in a 1990 letter to the editors of *The Atlantic* magazine, Dr. Daniel Steinberg, chairman of the conference that started the publicly funded National Cholesterol Education Campaign against cholesterol in the USA, declared that 100,000 lives could be saved each year. He further claimed that this non-fact had been demonstrated with statistical significance “*in a large number of studies.*”[\[153\]](#)

Just a few months later, Dr. Basil Rifkind, who had been the director of the LRC study, admitted in a medical journal that the scientific trials had not reduced the number of deaths from coronary heart disease and that “*further gains in life expectancy are unlikely in developed countries.*”[\[154\]](#)

The LRC results were so feeble that they may well have been caused by mere chance. And both the drug used in the study, cholestyramine, and the supposedly innocent placebo taken by the control group produced some extremely unpleasant side effects. Sixty-eight percent of the men taking the cholestyramine experienced gastrointestinal side effects during their first year of treatment: they had gas, heartburn, belching, bloating, abdominal pain, nausea, and vomiting, and almost fifty percent had constipation or diarrhea. In the control group during the first year, forty-three percent experienced similar side effects, a far higher rate than what occurs if the placebo is truly ineffective.

The readers of the report are reassured that the side effects were not serious and they could be neutralized by standard clinical means, and after seven years the number of these side effects had decreased to only twenty-nine percent. This was not more than after the placebo treatment. Their words suggested that the symptoms from the stomach and the guts had nothing to do with the cholestyramine treatment but was pure imagination or symptoms that the test individuals should have had also without treatment.

In controlled drug trials the control group is usually given an ineffective placebo. The reason is that symptoms considered as side effects may in fact be accidental symptoms unrelated to the treatment; symptoms which by chance appear during the treatment. Accidental symptoms may of course occur in the controls also. Therefore, the percentage of side effects in the placebo group are subtracted from the percentage of side effects in the treatment group to give the true percentage of side effects from the drug.

But here they had given a placebo which certainly not was without side effects; gastrointestinal symptoms in forty-three percent is much more than is usually seen after an innocent placebo. Therefore it is not reassuring to hear that the side effects from the drug equaled the side effects from the placebo.

Neither is it reassuring to learn that, “*the side effects were treated by standard clinical means.*” These words mean that more than half of these previously healthy individuals in addition to cholestyramine or placebo also took laxatives, antacids or drugs to stop diarrhea or to prevent nausea and vomiting.

A greater number in the treatment group were also admitted to hospital for operations or procedures involving the nervous system. No diagnoses or more specific information was given and as it was impossible for the experimenters to find a reliable explanation to the effect of cholestyramine on the nervous system these side effects were classified as coincidental. The authors did not consider that it should have been the lowering of blood cholesterol and not cholestyramine itself which had given rise to the side effects.

Few people know about the many side effects, which they may get by taking cholestyramine. One reason is of course that they are rarely mentioned to the public. For instance, read another sentence from the letter in *The Atlantic* by Daniel Steinberg: “*The drugs in current use for lowering cholesterol levels have remarkably few side effects and, to my knowledge, no fatal side effects.*”

Now we have definitely proved that it is worthwhile to lower blood cholesterol; no more trials are necessary. Now it is time for treatment. In short, this was the message from the experimenters of the LRC. And they considered treatment necessary for most people.

It is a prudent rule in clinical science to be careful with conclusions about other patient groups than those who have been studied, especially concerning a disease with large age and sex variations. If it had been shown (which indeed is questioned) that a treatment is beneficial for middle-aged men with an extremely high blood cholesterol, only this category should be treated until it has been proven that it is also beneficial for other categories of human beings.

In the LRC it was not even middle-aged men with high blood cholesterol who had been studied but to a great part men with inborn errors of cholesterol metabolism. You may probably recall that it was those with the upper 0.8 percent of the blood cholesterol values who had been selected for the trial. As almost one percent of mankind has an inborn abnormality of cholesterol metabolism most of the participants must have belonged to that category. Even if we presume that the treatment was useful it is not evident that a treatment that is useful for such individuals is useful for normal individuals as well.

But nothing was said about that in the paper, neither had the directors of the LRC trial any reservations. Not only middle-aged men should be treated but also other age groups; and not only men with a high blood cholesterol, but also those whose cholesterol was close to normal; and not only men, but also women although women

were not studied and although almost all previous studies had shown that a high cholesterol is not a risk factor in women, neither is treatment of any use. The only group that was not mentioned in the report was the children, but this was repaired later.

LRC was not designed to assess directly whether cholesterol lowering by diet prevents heart attacks, they wrote, but the results from the LRC trial taken together with the large volume of evidence relating diet, plasma cholesterol levels, and coronary heart disease, its findings support the view that cholesterol lowering by diet also would be beneficial.

This is a typical argument from diet-heart supporters. Taken together one by one no study has proven that animal fat and high cholesterol is dangerous to the heart, but if you put all the studies together, they do. In the Alice-in-Wonderland atmosphere of the Lipid Research Clinics, nothing plus nothing conveniently equals something.

Science by citation

The high rate of coronary heart disease in Finland has prompted several experimenters to conduct preventive trials; Dr. Tatu Miettinen and his coworkers from Helsinki are among them.

One-half of about 1200 middle-aged, more or less overweight and hypertensive male business executives with high blood cholesterol were advised about smoking, exercise, weight reduction and diet; the other half was used as a control group. If the blood pressure and the blood cholesterol in the treatment group did not become normal they were also treated with various blood pressure and cholesterol lowering drugs.

The experimenters were quite satisfied with the effects of their efforts on risk factors. Blood cholesterol fell by 6.3 percent, the blood pressure by about 5 percent and the tobacco consumption with about 13 percent.

But improved risk factors did not lead to better end results. In the group who exercised, reduced their weight, ate less animal and more vegetable fat, and had quitted smoking, twice as many heart attacks were seen as in the control group.[\[155\]](#)

The investigators believed that the greater number of heart attacks probably was due to clofibrate which some of them had taken, or perhaps to the drugs against high blood pressure. (What a frightening thought that drugs which are used on millions of people to lower the blood pressure or to prevent coronary heart disease could actually cause it instead.)

Their explanation does not jibe with the results of other experiments. In two previous British trials it was said that due to clofibrate the number of heart attacks had

decreased, and other studies have shown that the drugs used against high blood pressure *protect* against coronary heart disease.

The unfavorable result may simply have been due to the fact that the therapy is ineffective. Therefore, the outcome is determined by chance; in one trial the number of heart attacks is a little smaller, in another a little greater. But the diet-heart proponents prefer to look at the supportive studies only and ignore those that are not.

Science Citation Index was an interesting aid for scientists at that time. (Today the PubMed program on the web is even better.) Here you could see who had cited any scientific paper, how often, and where. Editors of medical journals make a point of the papers published in their journal being cited frequently. Frequent citation indicates influence and is prestigious, not only for journals but also for individual scientists. The number of those who have cited papers by Nobel Prize laureates took up many columns each year in the small-typed Science Citation Index.

It was interesting to open the Index and see how often the 1985 paper by Miettinen and colleagues had been cited. Let us compare it with the main report from the LRC trial also, published one year previously. Both papers dealt with the same subject and were published in the same journal and no one has questioned the honesty of the experimenters or the quality of the studies; at least not the Finnish one. Reasonably, they should have been cited almost equally often. That the LRC trial, at least according to its directors, was supportive, and the Miettinen trial was not, is unimportant because the aim of research is to find the truth, whether it supports the current theories or not.

Table 6a. Here you can see how often the two papers have been cited during the first four years after their publication.

| Years After Publication | Miettinen and coworkers | LRC trial |
|-------------------------|-------------------------|-----------|
| First year | 6 | 109 |
| Second year | 5 | 121 |
| Third year | 3 | 202 |
| Fourth year | 1 | 180 |

The table shows that scientists are like the rest of us; they forget what is awkward and recall only the pleasant memories. A useful quality in private life but nothing to further knowledge.

What do you want: a gastric ulcer or a coronary?

New cholesterol-lowering drugs require new trials. That the previous results were less successful than expected was due to the side effects of the drugs. The fewer deaths from heart disease were balanced by more deaths from other reasons, it was said. Others thought that the cholesterol was not lowered sufficiently.

The new drug gemfibrozil (Lopid®) is chemically close to clofibrate, but was considered more favorable because it lowers the total amount of cholesterol in the blood and at the same time increases the “good” cholesterol. This drug was selected for a new trial in Helsinki, Finland in a project led by Professor Heikki Frick.[156]

Once again investigators chose healthy, middle-aged men with high blood cholesterol. All participants were advised to quit smoking, to exercise and to loose weight; and half of them were given gemfibrozil, the others a placebo drug.

Also in this trial the number of deaths was equal in the two groups, but for the first time a statistically significant reduction of non-fatal heart attacks was seen after cholesterol lowering only. In the Oslo-trial the participants had quitted smoking and lost weight also; in the LRC trial the effect was not significant according to the usual statistical methods; and in the WHO-trial from 1978 the smaller number of non-fatal heart attacks were outnumbered by a greater number of fatal ones.

Has science proved that high cholesterol is the killer? May we use the trial of Professor Frick and his colleagues as an argument to lower cholesterol in a large part of mankind?

According to the diet-heart idea cholesterol is dangerous because it generates atherosclerosis. If this were true then a lowering of blood cholesterol should also influence other vascular diseases caused by atherosclerosis. However, in all the trials the end points used had been fatal and non-fatal coronary heart disease only.

In all the tables of the trials the reader will find a small group of patients classified as “other cardiovascular diseases.” In most trials the number in this category is a little greater in the treatment group. No great differences, but when the effect of the trial is close to the border of statistical significance, as it usually is in the cholesterol trials (when the effect is not directly negative) the small differences between the numbers of “other cardiovascular diseases” take on great importance. If all cardiovascular diseases including coronary heart disease are put together then the result is no longer statistical significant and the result is as before: no difference which could not have been caused by chance.

In addition the treatment gave unpleasant side effects. During the first year 232 or 11.3 percent of the treated individuals had gastrointestinal symptoms. Gradually the side effects abated. The report did not tell whether the test individuals became accustomed to the drug or whether they were treated with other drugs to combat the side effects as in the LRC trial. What we know is that in the treatment group 81 were operated upon

because of some gastrointestinal ailment, in the control group 53 only. Thus, if the difference in the number of heart attacks was real and not caused by chance the question is if you prefer an operation of your stomach or gall bladder, or a non-fatal heart attack, because the sum of heart attacks and operations was almost identical in the two groups.

It is a fact that even this trial failed to lower mortality from coronary heart disease and there was no difference between the total number of deaths either; if anything, more had died in the treatment group. But this is not the end of the Helsinki story.

An expedient byproduct

Parallel with the mentioned study of healthy men the Finnish researchers performed another experiment on men who already had had a heart attack. About 600 such individuals participated, all of them worked at the same companies as those in the original Helsinki study.[\[157\]](#)

The result after five year was disheartening. Seventeen of those who took gemfibrozil had died from a heart attack; compared to only eight in the placebo group.

Dr. Frick and his coauthors were eager to stress, that this difference was most probably a product of chance. In the summary of the paper they wrote: the number of fatal and non-fatal heart attacks did not differ significantly between the two groups.

They were right, because in contrast to their fellow-directors of the other trials they used the correct formula for determining the effect of a treatment, the two-sided t-test. If they had used the one-sided test as diet-heart supporters usually do when the allegedly positive effects are measured, significantly more had died in the treatment group.

But they had modified the result in another way. In the group “cardiac deaths” they had included a small group called “unwitnessed death.” That death is unwitnessed means that we do not know the cause of the death. It is not self-evident that an unwitnessed death is due to a heart attack and such deaths should of course have been classified otherwise.

If they had excluded the unwitnessed deaths there were more than three times more fatal heart attacks in the treatment group; sixteen against five. And this difference was indeed statistically significant.

The directors of the study admitted that the result was not “*in accord with previous experience,*” but they had a number of explanations.

As the trial was only “*an expedient byproduct*” of the original trial the number of individuals had been too small to give reliable results, they said. They were especially concerned about the low number of heart attacks in the control group. It was unlikely

that it reflected the incidence in the general population. Most probably the individuals in the control group by chance had been less affected by coronary atherosclerosis than those in the treatment group.

Short guts and long lives?

At the University of Minnesota Medical School the surgeon Dr. Henry Buchwald had a bright idea. He had noted that when the last part of the small intestine is taken away from a patient (because of cancer or another disease) his blood cholesterol level decreased sharply. The explanation is that much cholesterol and bile acid is taken up in this part of the intestine, and as cholesterol is used for the production of bile acid in the liver considerable amounts of cholesterol are lost in the stools after the operation. Could this same operation be used to treat patients with too much cholesterol in their blood?

In 1963 Dr. Buchwald and his team performed the first ileal bypass to lower cholesterol. At this operation the last third of the small intestine, the ileum, is cut and closed, and the open end of the upper two-thirds is connected with the large intestine. Many such operations have been performed since then, mainly on patients with familial hypercholesterolemia. Unfortunately, only few researchers have studied the effect of the operation in a controlled study.

Two of them were Dr. Pekka Koivisto and Dr. Tatu Miettinen from Helsinki, Finland. [\[158\]](#) Twenty-seven patients with familial hypercholesterolemia had this operation performed and after ten years their course was compared with twenty-seven control patients matched for a large number of the usual risk factors for coronary disease and treated with cholesterol lowering drugs only.

The ileal bypass was indeed effective, more effective than the drugs. The final level of cholesterol was 23 percent lower in the operated patients and the LDL-cholesterol was even “better.” But there was no difference as regards the outcome. After ten years five of the operated patients and four of the controls had died from a coronary, and three patients in each group had had a non-fatal coronary.

In spite of this disappointing result Dr. Miettinen and his colleagues recommended ileal bypass as a treatment against high cholesterol. They saw the operation as a partial success because those who had had a coronary in the bypass group had only lowered their cholesterol by only 25 percent while those who hadn't had a coronary had lowered their cholesterol by 33 percent. Obviously they meant that the lowering should have prevented these heart attacks had it been more pronounced.

But it is difficult to see how the cholesterol level had any importance at all, because in the control group the lowering was about ten percent both in patients who had had a coronary, and in those who had not, and cholesterol in controls who hadn't had a coronary was almost 20 percent higher than in the operated patients who had suffered

one. Thus, if anything, the bypass operation had induced heart attacks instead of preventing them.

Dr. Buchwald himself, the inventor of the bypass operation, has conducted the largest trial of ileal bypass. In cooperation with 23 colleagues and 51 advisers he studied more than 800 middle-aged patients, mostly men, who had had at least one coronary. Half of them were randomized to ileal bypass, the other half were controls.[\[159\]](#)

After ten years 32 in the surgery group had died from coronary heart disease against 44 of the controls. In all, 49 had died in the surgery group, 62 in the control group. These differences were far from statistical significance; they could have been due to chance. But in a subgroup analysis Dr. Buchwald and his co-authors found that if only those who had suffered a less serious coronary initially were considered, the difference was almost statistically significant. (But among those who had had a *more* serious coronary initially, *more* had died in the surgery group.)

There were other bright spots. In the control group there were more non-fatal coronaries, more attacks of severe angina, and many more patients underwent an operation to get a new coronary, a so-called coronary-artery bypass grafting. If all these events were taken together the difference between the two groups was highly significant.

Apparently a success. However, a study like this is of course neither single nor double blind. It is necessary to remind you of Professor Cornfield's and Dr. Mitchell's conclusion from their early overview of cholesterol lowering trials: open trials are successful, blind trials are not. To decide whether a patient has had a coronary or something else, or whether a patient should have a coronary graft or not is of course a highly subjective matter. You must be divine to avoid irrational motives from influencing your judgment in a million-dollars trial with so much glory and prestige at stake.

The authors argued that the higher rate of coronary grafting in the control group had improved their survival and blunted the trend toward a reduction in mortality in the surgery group. However, new coronaries may eliminate your angina, but most studies have shown that they do not prolong your life. On the contrary, a net excess of two deaths in the control group could be ascribed to complications of the coronary grafting, thus a further reduction of the difference.

Other complications were produced by the ileal bypass itself. Each year four percent had a kidney stone, a total of about 135 attacks at all, 14 had their gall bladder removed, and 57 had symptoms of bowel obstruction, 15 of whom required an operation. And there was more.

Lack of the ileum means not only loss of bile acid. When bile acid is lost the fats transported with the bile are lost also and make the stools frequent and loose. Loss of

fats means loss of calories. On average, ileum bypass patients had a weight loss of 5.3 kg (11.7 lbs).

You may probably recall Dr. Kannel's words about the "formidable risk" of coronary heart disease which is added by obesity. An ileal bypass is an effective treatment against obesity, and obese patients must therefore have been in great excess in the control group. It is difficult to know how many extra heart attacks among controls were due to obesity, but at least this bias should have been mentioned in the discussion and in the summary of the report.

Can atherosclerosis disappear?

Trials including thousands of individuals are laborious and of course utterly expensive. In recent years scientists have taken a shortcut. Instead of coronary deaths they have used regression of coronary artery disease as a measure of treatment effect. By regression they mean a widening or at least a less rapid narrowing of the coronary arteries as seen on coronary angiography. An increase of the mean diameter of the coronary vessels during treatment is said to be due to disappearances of atheromas, the scientific name of the vascular lipid deposits seen in atherosclerosis. Angiographic trials are much cheaper because much fewer test individuals are necessary and the result is possible to evaluate after a much shorter time.

Laboratory changes instead of number of deaths as a measure of treatment effect is called surrogate outcome. The term surrogate is used because it is not self-evident that laboratory changes can be translated to clinical effects such as lowering of mortality. It can be questioned also, if a widening of a coronary vessel seen on angiography means disappearance of atheromas and nothing else, but let me come back to this question a little later. Let us first have a look at the angiographic trials.

The National Heart, Lung and Blood Institute supports the diet-heart idea to one hundred percent. Together with the American Heart Association they administer more than 90 percent of all grants for cardiovascular research. Also on the American Heart Association they are convinced about the danger of cholesterol. In fact, most of those who have introduced the cholesterol campaign or have advocated it most vigorously are members, or have previously been members, of these institutions.

On the National Heart, Lung, and Blood Institute they decided to study the effect of cholesterol lowering directly on x-ray angiograms. To lower cholesterol they had chosen cholestyramine, the same drug that was used in the ongoing LRC trial. In five years 116 male patients with coronary heart disease and high blood cholesterol were treated; one half were given cholestyramine, the other half a placebo drug.[\[160\]](#)

The result was again disappointing. In the treatment group the coronary arteries widened a fraction of a millimeter in four patients, but they widened also in four of the untreated patients.

Before the trial had started the investigators had decided to analyze their results using the one-tailed t-test that is scientifically unacceptable if the outcome can be both positive and negative. On the National Heart, Lung, and Blood Institute however, they said, that it was OK to use it because the weight of laboratory and epidemiological evidence suggested that reduction of blood cholesterol would retard coronary artery disease. The result could only go in one direction.

If you haven't skipped too many chapters you will probably agree with me that the weight of laboratory and epidemiological evidence suggest nothing of the kind. Let me only mention that when the study they initiated was published in 1984 not fewer than seven controlled cholesterol lowering trials had resulted in an *increase* of coronary mortality in the treatment groups.

By using the one-tailed t-test and by putting the figures together in different ways the fifteen directors of the study headed by Dr. John Bressi found a combination that gave statistical support for the benefit of the treatment. They admitted that the result was not exactly what they had expected, but they returned in a further paper^[161] stating that the improvement was proportional with the changes of blood cholesterol they had seen in the patients independent of whether they had been treated or not. With other words, the coronary vessels had less often worsened if the cholesterol was low than if it was high.

It is easy for cholesterol researchers to get caught up in circular reasoning. We do not yet know the cause of atherosclerosis. What we do know is that high cholesterol is a risk factor. Theoretically high blood cholesterol may be the cause, but as I have said before high cholesterol may be secondary to the real cause; the causative factors may have induced atherosclerosis and at the same time it may have raised the level of cholesterol in the blood. The aim of the study was to see which of these alternatives were true by lowering blood cholesterol. Thus, the only valid finding is a possible effect of cholesterol lowering on atherosclerosis in the treated patients. If cholesterol is the bad guy a reduction in its concentration should be followed by a decrease in atherosclerosis, or at least by a halting of its progress.

If cholesterol is only an innocent bystander witnessing the crime and being influenced by it, then a reduction in its concentration would not have any effect because the unknown villain continues his activity. Crime is not prevented by killing the witnesses.

“Selective blindness”

Supported by the National Heart, Lung, and Blood Institute and the drug company Upjohn Dr. David Blankenhorn and his group started a new angiographic trial, called CLAS, the Cholesterol-Lowering Atherosclerosis Study.^[162]

This study included 162 patients who had undergone coronary bypass operation. After routine laboratory tests all major arteries in the bodies were examined by angiography. The patients were then randomly assigned to two groups of equal size. One group took cholesterol-lowering drugs, the other took ineffective placebo tablets. Neither the patients nor the doctors knew which group got treatment and which did not. To be sure that cholesterol was lowered properly, two drugs were given at the same time, colestipol and nicotinic acid.

After two years of treatment an angiography was performed again. In 16 percent of those who had been given the drugs but only in two percent of the control patients the coronary arteries had widened. In 38 percent of the treated patients the diameter of the vessels had decreased, but even this finding was seen as a success as the vessels had narrowed in still more of the controls, about 56 percent.

And the differences were statistically significant according to Dr. Blankenhorn and his colleagues, but only with the one-tailed test.

It may seem petty to take exception to the details of statistical formulas, and if the authors had underlined the weakness of their study and made reservations for the questionable results themselves no further discussion had been necessary. But the authors did not hint at any weakness. Their remarkable deviation from standard statistical practice was not even mentioned in the summary of the paper, nor when Blankenhorn's study was cited in other publications. Furthermore, there was another problem.

The side effects of nicotinic acid, one of the drugs used in the study, are so obvious that no one can have any doubt of who is taking the drug, least of all the patient. Shortly after having swallowed the tablet the patient feels his skin is burning and itching as if stung by nettles. No doubt, the patient will tell about the side effects to his surroundings, including his doctor.

If the doctors still wanted to know for certain whether the patient had treatment or not they could look into the laboratory records. To be sure that the cholesterol really went down all patients had eaten the drugs during a period of three months before the start of the trial, and those whose cholesterol did not go down as much as was anticipated were excluded.

And cholesterol went down. On average blood cholesterol decreased by 26 percent in those who took the drugs; the "bad" cholesterol decreased by as much as 43 percent. On their regular visits at their doctors the patients might as well have had a sign around their neck telling to which group they belonged.

Thus, the trial was neither single nor double blind, which the authors also admitted. They called it "selective blind"; a new, but striking description of the condition on the branch of the research tree where the cholesterol hawks are breeding.

A researcher may be utterly impartial and dedicated to the truth, but he is probably not a saint. All experience tells that if the doctors knew to which group the patients belonged, their judgement must have been influenced in at least some of the cases no matter how much they tried to avoid this bias.

But Dr. Blankenhorn's group was so certain of their results that they immediately called a press conference at the National Heart, Lung, and Blood Institute and with much fanfare announced their sensational findings.^[163] Now, at last, "*for the first time*" they had shown "*a strong and consistent therapy effect from cholesterol lowering at the level of coronary arteries.*"

Obviously, Dr. Blankenhorn had forgotten, that Dr. Brensike and his coworkers, claimed to have proven this several times. As you probably recall, it was Dr. Brensike's "*strong laboratory and epidemiological evidence that allowed them to use the one-tailed t-test.*"

But Blankenhorn went further. He also claimed that his study demonstrated, that blood cholesterol should be lowered to a level of 185 mg/dl and this was also the limit that was set at the National Heart, Lung, and Blood Institute and the American Heart Association after Blankenhorn's study. What an amazing perspective! Remember that even the strongest supporters of the diet-heart idea do not believe that diet is sufficient to lower cholesterol as much as in Blankenhorn's trial; instead drugs must be used. How many adults have blood cholesterol above 185 mg/dl (4.85 mmol/l)? According to Dr. Basil Rifkind, one of the strongest advocates for the diet-heart idea, it probably amounts to 40 million healthy Americans. Said Robert Levy, former head of the American Heart Association, the results were "exciting" even if they were not quite unexpected. And the directors of the drug producer, Upjohn Company must have been delighted.

In a scientific report, it is customary to include discussion of the results of other investigators, especially when they deviate completely from one's own results. How did Dr. Blankenhorn and his coworkers and the brain trust at the National Heart, Lung and Blood Institute comment on the disheartening results of Drs. Bemis, Kimbiris, Shuh, Kramer and their groups, who didn't find the slightest connection between changes in cholesterol deposits in the coronary vessels and changes in cholesterol levels in the blood? How did they explain the fact that the coronary vessels improved in their own experiments, but not in the many previous studies where cholesterol went down just as much or more? Why did they place more importance on their own dubiously positive results than on the many indisputable negative ones? I cannot give you an answer because they did not comment on them at all.

Something better

Three years later, in 1990, the results from a new angiographic trial was published by Dr. Greg Brown and his team in Washington, again supported by the National Heart, Lung, and Blood Institute.[164] Obviously they were not impressed by the “strong and consistent” effect of Blankenhorn's treatment. In their paper they wrote that the lipid changes in the previous trials were small and the clinical benefits limited. Therefore Dr. Brown and his colleagues had used two drugs at the same time. Thirty-eight men received lovastatin and colestipol, 36 received nicotinic acid and colestipol and 46 received placebo, and the trial was designed as a double-blind study. Most of the men participating had familial hypercholesterolemia.

And indeed cholesterol was lowered; by 34 percent in the lovastatin-colestipol group and by 23 percent in the niacin-colestipol group. The devil himself, LDL-cholesterol was lowered even more, by 45 percent and 32 percent, respectively.

Before and after treatment the width of the coronary arteries were measured at various points, using a fivefold magnification of the x-ray pictures. Magnification was necessary, because on average, the vessel diameters in the niacin-colestipol group increased by a mere 0.04 mm only, whereas the diameters in the lovastatin-colestipol decreased by 0.002 mm and in the control group by 0.05 mm. Indeed small differences, but they were statistically significant, and Dr. Brown and his colleagues saw them as a proof of therapeutic success.

I am sure you noticed that the vessel diameters *decreased* in those treated with lovastatin-colestipol, those who had their cholesterol lowered the most. In some places of the arteries the diameter had increased, but on average, taking all measurements together, the diameters had decreased. A decrease of the diameters means of course that the coronary vessels had become narrower, which is certainly not an improvement, although the diameter in the control group decreased even more. The authors had no comments about this striking finding, neither about the fact that the only two deaths in the study, and the only heart attack, were seen in the lovastatin-colestipol group. In fact, the title of their paper said the opposite: “*Regression (improvement) of coronary artery disease as a result of intensive lipid-lowering therapy...*”

The anguish of angiography

Let us still have in mind, that a change of the coronary diameter is nothing but a surrogate outcome. It is assumed that a widening of a coronary vessel on an X-ray means less atherosclerosis and thus a better chance to avoid a heart attack, but this is only an assumption.

Artery walls are surrounded by smooth muscle cells. When such cells contract, the artery narrows. When they relax, it widens. Various factors may stimulate the smooth muscle cells of the coronary arteries. Most important, mental stress, anxiety, exposure

to cold, and even a sustained handgrip may lead to contraction. The latter effect was studied six years earlier by Dr. Greg Brown, the same Dr. Brown who led the angiographic trial mentioned above.[165] He found that a handgrip sustained for a few minutes was followed by a 35 percent decrease of the vessel diameter.

Consider that the changes seen in the trials were only a few percent on average. What do you think you would do yourself if somebody were to put a long catheter all the way from your groin up to your heart and into your coronary vessels? If you are not a stuntman or an astronaut I think that you probably would have gripped the nurse's hand or something else very tightly, at least during the first examination. How, then, did the researchers know whether an increase in blood vessel diameter at the second examination was due to the patient being more relaxed or to the vessels being less atherosclerotic?

Also, drugs which relax the coronary vessels, and which are used by almost all coronary patients, may have disturbed the study. In the trial Dr. Brown and his coworkers were aware of that problem. The use of such drugs was "*duplicated as exactly as possible*." This can't have been too easy because the level of any drug in the blood depends on a large number of factors which are difficult to standardize. And Dr. Brown and his colleagues didn't write anything about duplicating possible handgrips or anxious feelings because such duplication is, of course, impossible. So, any factor which may influence the state of the smooth muscle cells in the coronary vessels may have influenced the vessel diameter much more than the possible appearance or disappearance of a tiny amount of cholesterol.

There are more uncertainties. Dr. Seymour Glagov and his colleagues from University of Chicago studied the hearts of 136 deceased individuals and found that when vessels become sclerotic, they widen to compensate for the narrowing brought about by the deposition of cholesterol in their walls. In fact, this widening overcompensates for the deposition until the cholesterol deposits occupy about 40 percent of the area beneath the muscle wall.[166] Only thereafter does the vessel become steadily narrower. In other words, an increase of vessel diameter may be due to disappearance of cholesterol in a highly sclerotic vessel, but also to a compensatory widening during the first stages of cholesterol deposition. How could the trial directors know whether the increase of vessel diameter was due to a disappearance of deposited cholesterol, or to a compensatory widening due to an appearance of deposited cholesterol?

Risk factors and coronary vessel

The fact, that a lowering of cholesterol may reverse sclerotic lesions also conflicts with the results from a number of previous, angiographic long-term studies of the coronary arteries. The aim of those studies was to explore which factors dictated the development of atherosclerosis. Were the risk factors primary or secondary? Should they be sought among the mercenary troops or were they something which followed

the vestige of war as hunger and cholera? Was smoking of any importance? Did the blood pressure influence the development of atherosclerosis? Did a high blood cholesterol?

According to the conventional wisdom, atherosclerosis should increase if the cholesterol over a longer period of time is high or if it goes up, no matter why. Likewise, atherosclerosis should decrease, or at least it should not increase, if cholesterol is low or if it goes down.

One of the first who studied the inside of the coronary vessels with such questions in mind was Dr. Charles Bemis. The year was 1973. Together with his team at the Peter Bent Brigham Hospital in Boston[167] he studied about seventy patients and found that the only factor which could be connected with the degree of atherosclerosis was the level of the blood lipids at the start of the investigation. In patients with high blood cholesterol at the start, coronary atherosclerosis had increased at the following angiographic examination a couple of years later.

So far, the results were as anticipated. Once again, it was demonstrated that high blood cholesterol is a risk factor for coronary heart disease. Now to the interesting finding.

In twenty-four patients, cholesterol had decreased by more than 25 percent between the two angiographies, a lowering which was considerably greater than in most cholesterol lowering trials. Among these twenty-four patients, atherosclerosis had increased in sixteen, while it was unchanged in just eight. In twelve patients cholesterol had increased, but only in four of them had atherosclerosis increased.

Said in another way: two out of three whose cholesterol went down had become more sclerotic, while this was the case in only one out of three whose cholesterol went up. It should, of course, have been the other way around.

Dr. Bemis's result was confirmed the following year by Dr. Demetrios Kimbiris and his group in Philadelphia.[168] These investigators also found that cholesterol was unimportant. The coronary arteries of seventeen out of twenty-five patients with high cholesterol had worsened, but they had also worsened in seven out of ten patients with a low cholesterol.

Similar results were achieved at the famous Mayo Clinic by Dr. Clarence Shub and his colleagues. They found that coronary atherosclerosis had increased in all patients whose cholesterol had decreased by more than 60 mg/dl, a lowering which should have been considered more than acceptable in any cholesterol-lowering trial.[169]

In study after study the startling finding of Bemis and his colleagues was confirmed. [170] In their paper, Dr. John Kramer and his colleagues at the Departments of Cardiology and Biostatistics, The Cleveland Clinic Foundation, concluded: "... medical treatment directed toward 'secondary prevention' may be unsuccessful in

retarding or reversing the development of progressive arterial lesions and their clinical consequences.”

But nobody listened. More prudent scientists should have questioned the diet-heart idea, facing the fact that coronary atherosclerosis is worsened just as fast or faster when cholesterol goes down as when it goes up.

In a scientific report it is a rule to discuss also the results of other investigators, especially when they deviate completely from one's own results. How did Blankenhorn and his coworkers and the brain trust at the National Heart, Lung, and Blood Institute comment on these disheartening results? How did they explain that the coronary vessels improved in their own experiments, but not in the many previous studies where cholesterol went down just as much or more? Why did they place more importance on their own dubiously positive results than to the many indisputable negative ones?

I cannot give you an answer because nothing was said about them.

Recently, a team led by Canadian Dr. David Waters published yet another study including 335 patients.[\[171\]](#) They found that when the coronary vessels after a two year interval had narrowed by more than 15 percent, the risk for cardiac death or a non-fatal coronary increased considerably. Certainly not an unexpected finding. Their conclusion was that the changes seen on coronary angiography was a good substitute for cardiac events in clinical trials.

But they didn't comment that on average the cholesterol of those whose atherosclerosis had progressed did not differ significantly from the cholesterol of those whose atherosclerosis had not progressed. Remember that the cholesterol in the angiographic trials went down by 30-49 percent, but the change of the vascular diameter was much less than one percent. In Waters's study the diameter change was more than 15 percent, but the decrease of cholesterol an insignificant two percent. Such results do not suggest that the diameter changes have anything to do with the cholesterol changes.

Meta-analysis

Certain treatments are easy to assess. The right antibiotic, for instance, will cure nine out of ten women with an uncomplicated urinary infection, which means that after having treated fewer than a dozen patients and controls for a few days you already know for certain that the drug is effective. But after the many cholesterol-lowering trials, scientists still don't know whether the treatment could change mortality. Statisticians say that to prove a beneficial effect on mortality, many more test individuals are necessary, probably more than 100,000. If the beneficial effect of treatment is so difficult to prove, aren't we justified in concluding that high cholesterol cannot be that dangerous for our health?

But the problem may be solved in another way. The solution is called meta-analysis.

In a meta-analysis, data from all studies that satisfy certain standards of quality are put together in the hope that they will provide a large enough sample for statistical reliability. For medical trials, at least, three standards are mandatory. Trials should be double-blind, they should be controlled, meaning that on average, all risk factors are similar in the two groups, and the test individuals and the controls should be chosen randomly. Also, in order to use the accumulated results from many trials, it is necessary for the same kind of treatment to have been used in each trial and, of course, the result of the treatment—the outcome or the end point—should also be the same.

By now you may have realized that if all standards are to be satisfied, very few trials can qualify. Very few trials have been performed in a true double-blind fashion, and besides cholesterol-lowering, some trials have also used other kinds of intervention. Nevertheless, let us have a look at the entire body of trials that have been published before 1992, all of them performed before the introduction of the statins.

Several meta-analyses on cholesterol-lowering trials have been published. When I prepared the first edition of this book in Swedish it annoyed me that most of these analyses had excluded a number of trials, preferably the unsupportive ones. So I decided to perform a meta-analysis myself that included all randomized and controlled trials where the aim had been to lower cholesterol, whether by diet, or by drugs, or whether they had used other kinds of intervention also.^[172] I accepted open trials, since it was not possible to do a fair selection of double-blind studies because even trials that were designated double-blind were in fact more or less open for the reasons I have given above. In table 6B the raw figures from this analysis are given.

Table 6B. Overall result of 26 controlled cholesterol-lowering trials. The number of individuals in the three calculations are not identical because a few trials did not give the number for all end points.

| | Treatment Group | Control Group |
|-----------------------------------|-----------------|---------------|
| Number of individuals | 59,514 | 53,251 |
| Non-fatal heart attacks (percent) | 2.8% | 3.1% |
| Number of individuals | 60,824 | 54,403 |
| Fatal heart attacks (percent) | 2.9% | 2.9% |
| Number of individuals | 60,456 | 53,958 |
| Total number of deaths (percent) | 6.1% | 5.8% |

As you see, the number of deaths from a heart attack was equal in the treatment and in the control groups, and the total number of deaths was greater in the treatment groups. In one study total mortality had decreased significantly, in two others it had increased significantly, and in no trial was coronary mortality changed more than could be attributed to chance. More sophisticated calculations did not change the picture.

There was a small reduction in the number of non-fatal heart attacks. Calculated in the way diet-heart supporters usually do the difference was 10.4 percent; calculated the simple way, the difference was 0.3 percent. Due to the large number of individuals studied this small difference was statistically significant, but most probably it was a result of bias. Not only were the trials open and partly multifactorial; there was another finding that definitely proved that cholesterol lowering does not make any benefit.

If cholesterol lowering could reduce the risk of coronary heart disease, a pronounced and prolonged lowering should of course lower the risk more than a slight and short one. But there was no relationship between the degree of cholesterol lowering and any of the end points, not between individuals in each trial and not between trials. And on average, total mortality was equal in short and long trials, and coronary mortality was *higher* in long trials than in short ones.

So, although some of the trials also included physical exercise, weight loss, reduction of blood pressure, and smoking advice, and although most trials were open, the number of non-fatal heart attacks was not reduced by more than 0.3 percent. And even if the doctors had been totally uninfluenced by their knowledge about the patients' group affiliation, remember that what doctors—even experienced ones—call a heart attack very often is something else.

After its publication in the *British Medical Journal*, my meta-analysis provoked harsh comments from diet-heart supporters.^[173] According to my critics, the most serious mistake was to include trials using hormones, since such drugs are now considered toxic to the heart. But in one of the first controlled trials published, conducted by Professor Jeremiah Stamler, the researchers used low doses of the female sex hormone estrogen and that trial had the best result of all. High doses of estrogen are possibly harmful for men, but whether low doses are harmful is an open question. In women, at least, low doses, such as those used in post-menopausal hormone replacement therapy, seem to protect against heart attacks.^[174] The results were also just as unsupportive in the subgroup calculations, even in subgroups that did not include the hormone trials.

Another objection was that I had ignored the angiographic trials, because they “can lead to regression of atheroma,” as one of the critics noted. Let us therefore look at a more recent meta-analysis which included the angiographic trials.

In this analysis, Dr. George Davey Smith at the Department of Public Health, University of Glasgow, Scotland, and his coworkers excluded the multifactorial trials to study the effect of cholesterol lowering only, and they limited their analysis to total mortality.^[175] They ranged the trials in order of risk according to the coronary mortality in the control groups. In high-risk trials, many control individuals had died from a heart attack, in low-risk trials relatively few.

In the high-risk trial group (including 5,115 individuals in ten trials on the uppermost part of the risk list) mortality had decreased. In the median-risk group (including 24 090 subjects in 15 trials), mortality was unchanged. In the low-risk group, the largest one (including 27,918 subjects in ten trials on the lower-most part of the list), mortality had increased. Both the decrease and the increase of total mortality was statistically significant. Overall, in trials where drugs had been used to lower cholesterol, mortality from non-coronary causes had increased significantly. The authors' conclusion was that benefits from cholesterol lowering drugs seem to be produced in only a small proportion of patients at very high risk of death from coronary heart disease. Thus, in the future cholesterol lowering should include only individuals at very high risk. But here a problem appears.

Individuals in the so-called low-risk group were only at low risk compared with individuals in the other two groups. In comparison with normal individuals, they were at high risk also. For instance, their cholesterol was 278 mg/dl (7.13 mmol/l) on average, higher than in the other two groups! Remember that at that time the lower limit for drug treatment according to the early recommendations of the National Heart, Lung, and Blood Institute was 185 mg/dl (4.75 mmol/l); according to the cholesterol campaign it was 240 mg/dl (6.15 mmol/l). Furthermore, half of the trials in the so-called low-risk group were of the secondary preventive type, which means that they included patients who already had suffered a coronary. Such patients always have been considered as being at high risk. Many of the individuals in the low risk group were exposed to other risk factors also, so indeed this group was a sample of high-risk individuals. How should we discriminate between these high-risk individuals and the high-risk individuals who are said to prosper from cholesterol lowering? The simple fact is that we can't. Even doctors who treat high-risk individuals only may shorten the lives of their patients instead of prolonging them.

It is also questionable if mortality really was lowered in the high-risk trial group. One of the trials for instance, was in fact a multifactorial trial that had been included by mistake. The good result in that trial could therefore have been caused by something other than cholesterol lowering. The other trials were very small, and in only one of them was mortality lowered significantly. There was only one reasonably large trial in the high-risk group, but in that trial mortality had *increased*.

Anyone who has read scientific papers or official recommendations about cholesterol and the heart know that we are told another story. Listen, for instance, to the most

recent recommendations of the *European Atherosclerosis Society*: “Clinical trials of secondary prevention by lowering plasma cholesterol, when studied together by meta-analysis, show that morbidity and mortality from coronary disease are reduced; there is also a trend to lower total mortality.”[176]

This misleading statement is not unique; in fact, it is typical of diet-heart writings. Similar statements are found in numerous scientific papers from the supporters, and from the mass media.

There is more than one explanation for the inappropriately optimistic messages from doctors and scientists. Most important, scientists prefer to cite only the supportive trials. I have already told about the few citations from the unsupportive trial by Miettinen and the many citations from the allegedly supportive LRC trial. On average, I found that trials considered supportive by their directors have been cited almost six times more often than unsupportive trials.[52] The fact that a trial was cited frequently had little to do with its quality or whether it had been published in a famous or a less well-known journal. The trial directors themselves were especially unwilling to cite an unsupportive trial; since 1970 up to 1992, no trial considered unsupportive by its directors had been cited in another trial report. Even authors of meta-analyses had selected their trials according to their outcome.[54]

A successful dietary trial

The idea that a Mediterranean diet—whatever that is—would be beneficial for cardiovascular disease inspired the French researcher Dr. Michel de Lorgeril and his team from Lyon, France, to start a new dietary trial, the Lyon Diet-Heart study.[177] About 600 patients who had survived a first heart attack were included. Half of the patients were instructed to adopt the so-called Mediterranean diet by including more bread, more root and green vegetables and more fish, and by reducing consumption of animal fat and red meat. They were also instructed to eat fruit every day, to replace pork with poultry and to replace butter and cream with margarine, which was supplied free for the whole family. In contrast to the previous trials, where the dietary fat was dominated by vegetable oils with a high content of omega-6 polyunsaturated fatty acids, these researchers used a margarine made with rapeseed oil, which has a high content of α -linolenic acid, a polyunsaturated fatty acid of the omega-3 class. This special type of margarin was supplied free for the whole family. Control group individuals were also given dietary advice, but were recommended the usual “prudent” diet.

This design was chosen because in a previous study people from Crete, the Greek island where heart attacks were rare according to the Seven Countries study, had three times more of this fatty acid in their blood than the people from Zutphen, the Netherlands. The French researchers therefore thought that α -linolenic acid might be

protective because the rate of heart attacks was much higher in Zutphen than on Crete although their cholesterol levels were almost identical.

After forty months, a significant difference was found; in the control group 20 individuals had died, compared to only eight in the treatment group. Most surprising was, that in the control group eight of the patients who died from a heart attack had died suddenly, which almost always means that they have died from a disturbance of the heart rhythm. This was not seen in any of those who died in the treatment group. After four years the trial was ended because the improvement in the treatment group had continued; 24 had died in the control group but only 14 in the treatment group. And the difference between the number of nonfatal heart attacks was even larger—25 in the control group, but only eight in the treatment group—and it was therefore considered unethical to continue the trial.

For the first time a dietary trial had succeeded in lowering the risk of dying from a heart attack. Evidently it was a good idea to lower cholesterol by dietary means.

But blood cholesterol was practically identical in both groups after the trial had ended. In fact, it was a little higher in the treatment group.

If the difference couldn't be explained by the participants' cholesterol, what else could? Was it the additional α -linolenic acid or was it the extra fruit or vegetables? Or the extra bread? Or the extra fish or chicken? Or, as both fish and α -linolenic acid is rich in omega-3 polyunsaturated fatty acids, perhaps a better balance between omega-3 and omega-6 polyunsaturated fatty acids? According to the food frequency questionnaire at the end of the study the intake ratio of omega-6/omega-3 in the control group was about 20/1, in the intervention group about 4.5/1.

There is much evidence, both from animal experiments and epidemiological studies that a high ratio between omega-6 and omega-3 polyunsaturated fatty acids may predispose to heart arrhythmia, the main cause of sudden death in patients with heart disease. A few years later a new trial gave further support to that idea.

The GISSI-Prevenzione trial

One of the largest controlled, dietary trial was started in Italy, named Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico Prevenzione trial, or GISSI. [178] More than 11,000 patients who had survived a first myocardial infarction were enrolled and divided into four equally large groups. One group were treated with a capsule containing a mixture of three different omega-3 polyunsaturated fatty acids, one group a capsule with vitamin E, one group were given both capsules, and the fourth group was used as control. All of them received standard treatment for coronary patients.

On average the patients were followed for 40 months. At follow-up 3.5% in the control group had died from sudden death, 2.3% in the vitamin E group, 2.4% in the combined group, and 1.9% in the omega-3 group. Except for the result in the vitamin E group these differences were statistically different; indeed, the difference between the control and the omega-3 group was greater than in any of the following statin trials. Relatively seen, mortality due to sudden death was 46% lower than in the control group. Also the total number of deaths was significantly lower, and again, no differences were seen between the groups as regards blood cholesterol.

Interestingly, no differences were seen between the number of non-fatal heart attacks, a further argument for the idea that the omega-3 polyunsaturated fatty acids primarily protect the nerve conduction system of the heart.

Those who still believe that high cholesterol is the main villain perhaps may argue that the disappointing results from the trials I have discussed in this chapter may be because we haven't lowered cholesterol sufficiently. But to-day we have got a pharmaceutical method to lower cholesterol much more than by using any of the previous drugs; the statins. And according to the directors of the statin trial intensive cholesterol lowering by statin treatment is harmless and also an effective means to prevent cardiovascular disease.

“The most exact data base”—the screenees of MR.FIT

The figures from the MR.FIT study included both the 12,000 participating men, but also the more than 300,000 men who were excluded for various reasons. A large number of studies concerning the follow-up of these screenees has been published in well-known international medical journals, and these studies are cited again and again as the strongest proof that there is a linear association between blood cholesterol concentrations and the risk of future heart disease.

Unfortunately, the data presented in the MR.FIT reports have been carelessly produced. In a systematic search of the literature on the MR.FIT study, Professor Lars Werkö, then director of the Swedish Council on Technology Assessment in Health Care, an independent governmental agency known for its integrity, found 34 papers reporting the relationship between serum cholesterol and mortality. He asked himself whether it really was necessary to publish all these reports as their results were so similar.

“Have the editors really judged the original scientific value of each of these similar articles and deemed them worthy of publication? Or have they been impressed by the status of the research groups that authored these repetitive manuscripts, with the prestigious National Heart, Lung and Blood Institute in the background, and found that they have to succumb to the authorities?”

Worse than being repetitive, the data were inconsistent and highly questionable. For instance, the number of screenees varied greatly between the studies, from 316,099 to 361,266. In particular, Professor Werkö was critical of the studies reporting how many had died and why, because it is highly unlikely that all of 361,266 individuals could have been tracked after 6-12 years.

How the cause of death had been established was not reported but we can be rather confident that most of the reported causes were based on death certificates written by general practitioners. Not only is the information from death certificates highly unreliable, but, in many cases (between 6 and 20 percent, depending on the report), death certificates were actually

missing. Yet some of the reports gave a detailed list of diagnoses for almost all deaths.

Furthermore, during the initial screening it came to light that one of the participating centers had falsified its data to increase the number of participants in the trial, possibly in order to obtain more financial support from the National Institutes of Health. This embarrassing matter received little mention in the follow-up reports, nor did the study authors mention the possibility that data falsification could have occurred in other centers as well. Instead, all discussion of the issue of quality control was studiously avoided. Wrote Professor Werkö: *“In the many publications regarding the MRFIT screenees, it is obvious that the authors are more interested in the mathematical treatment of large figures than in the quality of these figures or how they were obtained.”*

In spite of all these irregularities, the follow-up reports on the MR.FIT screenees are still cited as “the most exact database regarding the relation of risk factors to mortality in the healthy male US population.”

Werkö L. Analysis of the MRFIT screenees: a methodological study. Journal of Internal Medicine 237, 507-518, 1995.

Myth 7: The Statins – God’s Gift to Mankind

It's easier to fool people than to convince them they have been fooled

Mark Twain

In the late 1980s, the pharmaceutical companies introduced a new type of cholesterol-lowering drug called the “statins.” These drugs inhibit the body’s production of many important substances, one of which is cholesterol.

Sold as Zocor®, Mevacor®, Pravachol®, Lipitor® and Lescol® these new drugs have received wide acclaim because of their supposed lack of serious side effects and, in particular, because of the substantial cholesterol they can achieve. Whereas the earlier drugs could lower cholesterol by 15-20 percent at most, the statins can lower it by 30-40 percent or more. As of January 2000, the results from the large controlled, randomized and double-blind studies, including more than 30,000 test individual, and numerous angiographic trials have been published. More data will come.

Most doctors believe that the outcome of these trials is a victory for the cholesterol hypothesis. However, a closer look reveals that the cholesterol lowering effects are unimportant and actually rather a drawback.

Furthermore, the benefits are trivial and if present, only apply to certain patient groups. In addition, by process of statistical manipulation, ingenious criteria for selecting the test individuals, and generous limits to what are considered as normal laboratory results, the directors of the trials and the drug companies have succeeded in belittling the side effects and thus presenting the statins as harmless.

4S—The Scandinavian Simvastatin Survival Study

In 1994 the results from a large Scandinavian, multi-center trial using simvastatin (Zocor®) were published.[\[179\]](#) These results were noteworthy, indeed. For the first time a trial had succeeded in lowering the risk of both fatal and nonfatal coronary heart disease, and even total mortality. The results were heralded in the *British Medical Journal*: “*Lower patients’ cholesterol now! There is no longer any doubt about the benefit and safety*

of treating hypercholesterolemia in patients who have had a myocardial infarction.”

The results of the 4S trial were published in *The Lancet* on November 19 and presented on the same day at a press conference arranged by the producer of simvastatin and sponsor of the trial, Merck Sharp & Dohme. Present at the conference were the discoverers of the deficient LDL-receptor in people with familial hypercholesterolemia, Nobel Prize winners Joseph Goldstein and Michael Brown who, according to a Merck representative, proclaimed: “*This is Christmas Eve!*”

Their excitement is understandable; they must have had many sleepless nights thinking about the many disappointing results from the previous cholesterol-lowering trials. In the vigorous marketing campaign that followed, 4S was heralded as the *milestone trial* and simvastatin as *the missing link*.

The study was performed in cooperation with 94 Scandinavian medical departments and directed by Dr. Terje Pedersen from the cardiology section at Aker Hospital, Norway. The steering committee and monitoring staff also included employees from Merck, and all data from the trial were processed without outside supervision at Merck’s laboratories in the US.

Altogether 4444 men and women with a previous heart attack were treated, half with simvastatin, half with a placebo. After 5.4 years, 8.5 percent had died from a heart attack in the control group, compared with 5 percent in the treatment group. (Table 8A.) This improvement included men only; the number of women who died from a heart attack was equal in both groups, or to be more correct, a little more women died in the statin group.

But there were other benefits. The number of nonfatal heart attacks was lowered even more, from 22.6 percent in the control group to 15.9 percent in the simvastatin group, a gain of 6.7 percent. Furthermore, the number of strokes was reduced significantly, from 4.3 percent to 2.7 percent.

Curiously, in the following, even larger HPS trial[\[180\]](#) the results were only half as good as in 4S although it was the same drug and the same dose that was tested on the same type of participants, and although cholesterol was lowered just as much.

However, it is the figures from the 4S trial that are used in the marketing of Zocor, and they are expressed as percentages, not as percentage points. More about that in the following.

CARE, the Cholesterol and Recurrent Events Trial

A similar study, the CARE trial, conducted by Dr. Franck Sacks and his co-workers from seven American, Canadian and British university hospitals, used pravastatin (Pravachol®) to lower cholesterol, again in patients with a previous heart attack.[\[181\]](#) After five years, 5.7 percent had died from heart disease in the control group, compared to only 4.6 percent in the treatment group. Considering the large number of participants, this result doesn't seem particularly impressive and, indeed, it was not statistically significant either. In fact, the reduction in heart disease deaths was offset by more deaths from other causes.

There were other benefits, however. As in the 4S trial, the number of strokes was smaller in the treatment group, and there were also fewer nonfatal heart attacks.

WOSCOPS, the West of Scotland Coronary Prevention Study

The two statin trials mentioned above studied the effect on patients who already had heart disease. Is it possible as well to prevent heart disease in healthy individuals whose only "disease" is high cholesterol? This was the question asked by Professor James Shepherd and his team from the University of Glasgow, Scotland.[\[182\]](#) To that end they assigned more than 6,000 middle-aged men with average cholesterol levels to receive either pravastatin (Pravachol®) or a placebo drug in a new trial, called WOSCOPS, the West of Scotland Coronary Prevention Study. Although the effect of that trial was trivial and as well could have been due to chance, no one expressed any reservations about cholesterol lowering in healthy people. If your cholesterol is high it doesn't matter how healthy you are. Lower your cholesterol!

AFCAPS/TexCAPS, the Air Force/Texan Coronary Atherosclerosis Prevention Study

Is it possible to prevent heart attacks in healthy individuals with normal cholesterol? If so, it would mean that all of us would benefit from taking a

statin drug, starting at middle age and continuing for the rest of our lives. The economical ramifications are breathtaking, both for the stockholders of the drug companies and, in a less pleasant way, for the directors of health care systems all over the world, which would pay the bill.

A new statin trial called the Air Force/Texas Coronary Atherosclerosis Prevention Study, or AFCAPS/TexCAPS was organized to answer this question. It was directed by the former president of the American Heart Association Professor Antonio Gotto from Cornell University, New York, and his co-workers from various institutions and hospitals in Texas. Three of the co-workers were employees at Merck & Co., the company whose drug lovastatin (Mevacor®) was tested in this trial. More than 5,000 healthy men and almost 1,000 healthy women with no signs or symptoms of cardiovascular disease were assigned to treatment, as usual half with the drug, half with a placebo.[\[183\]](#)

After five years 2.4 percent had died in the treatment group, but only 2.3 percent in the control group. But as the trial directors proclaimed, the primary target in this trial was not to lower mortality, but to reduce the number of fatal and nonfatal heart attacks, and by classifying angina as a non-fatal event, the trial was indeed a success on that point.

LIPID, the Long-term Intervention with Pravastatin in Ischemic Disease study

Another pravastatin trial named LIPID included patients with previous heart disease with all ranges of cholesterol levels. This is a logical approach because the statins were found to prevent cardiovascular disease whether the cholesterol is high or low, therefore there was no reason to look at people's cholesterol at all.

This trial was conducted by Drs. Andrew Tonkin and John Simes at the University of Sydney, Australia, along with a team of 63 other researchers. Three of the co-workers came from the drug company Bristol-Myers Squibb, the sponsor of the trial.[\[184\]](#)

After six years 14 percent had died in the control group, but only 11 percent in the treatment group. There was also a small effect as regards heart mortality, but these effects were seen in men only. And as mentioned, the benefit was gained, whether their initial cholesterol was high or low, a

finding the researchers noted with much satisfaction. Obviously they didn't realize that this finding was a serious challenge to the very idea about dangerous cholesterol.

How do you explain that cholesterol lowering is beneficial in people with normal cholesterol if normal cholesterol is not a risk factor? By changing the definition of normal, of course. Today the authorities believe that all of us have too much cholesterol in our blood and, if there are other risk factors present, that this cholesterol should be forced to its knees, even if it is already low.

Summing up

First, the statins were almost as effective for women as they were for men. Indeed in the CARE trial the effect was most pronounced for the female sex, although almost all studies have shown that high cholesterol is not a risk factor for women.

Second, in several of the trials, the effect was independent of age, although almost all studies have found that high cholesterol is not a risk factor in old people.[185]

Third, patients who had suffered a heart attack were protected even though most studies have shown that high cholesterol is a weak risk factor, if any at all, for those who have already had a heart attack.[186]

Fourth, the number of strokes was reduced after statin treatment, although all studies have shown that high cholesterol is a weak risk factor for stroke, if any at all.

Most important, there was no association between the degree of cholesterol lowering and the outcome, the benefit was independent on the degree of cholesterol lowering. Atherosclerosis is allegedly caused by high cholesterol in the blood; the higher cholesterol is, the greater is the risk, and the more we lower cholesterol, it is said, the more benefit will we achieve. The most important proof of such a hypothesis is therefore an association between the degree of cholesterol lowering in the blood and the outcome of the lowering. Such an association is called exposure-response. (A similar term is dose-response, which means that there is an association between the dose of an added factor to a medium, in this case the dose of the drug given

to a patient, and the effect of that dose, in this case the outcome of the disease.)

Presence of exposure-response between degree of cholesterol-lowering and outcome doesn't prove causality, because the concentration of cholesterol may be secondary to the real cause, but absence of exposure-response definitely disproves it. Curiously, only a few of the clinical trial reports included a calculation of exposure-response.

From the CARE trial the lack of exposure-response was documented in a separate paper, and the authors' words left no doubt: "...in a multivariate analysis that included LDL concentration during follow-up, the change of LDL from baseline, expressed either as a percentage or absolute change in concentration, was not found to be significantly related to coronary events." [187] Put in plain words, benefit was seen whether cholesterol went down very much or only a little.

Many words were used to clarify this unexpected finding. The most likely explanation, that LDL has nothing to do with cardiovascular disease, wasn't mentioned, of course.

The directors of the WOSCOPS trial came to the same conclusion: "... *there was no obvious correlation between percent LDL reduction and event rate.*" Their conclusion was that the statins must have other beneficial effects. [188]

It is easy to calculate exposure-response once all the trial data have been recorded and tabulated. I leave it to the reader to speculate why it hasn't been done in the many clinical trials that followed. But in conflict with these results, many authors claim that the trials did show exposure-response. Their argument is based on an association between the mean degree of cholesterol lowering and the outcome in each trial. But presence of exposure-response demands that individual values are used in the calculation.

How come the statins are effective for individuals for whom cholesterol is not a risk factor? And how come the effect of the statins does not depend on how much they lower blood cholesterol? If the cholesterol level for these people is not a risk factor for heart disease, how could a lowering of that cholesterol improve their chance of avoiding a heart attack? If the level of

our cholesterol is so important, as we have been told for many years, why doesn't it matter whether we lower it by large or small amounts?

It is obvious that the statins have other, more beneficial effects than cholesterol reduction, and this was also the conclusion of the WOSCOPS trial directors. Statins lower the risk of individuals for whom cholesterol is not a risk factor and their effect does not depend on how much they lower blood cholesterol.

When the results from the 4S trial were presented to Swedish doctors, one of the findings was the lack of exposure-response, both for total and LDL-cholesterol. I was present at two of the meetings and pointed out this striking deviation from the cholesterol hypothesis. On both occasions, it was obvious that the speaker had not recognized the implications of this phenomenon. It was not mentioned either in the first report published in *The Lancet* in 1994. Therefore I sent a manuscript to *The Lancet* presenting the above arguments and several more. The paper was rejected by the editor Robin Fox with the following words:

Dear Dr, Ravnskov

I was not surprised to hear from you about the 4S study. The article gave rise to some useful correspondence, and it is clear that the argument about cholesterol and heart disease is not yet over. We need more data, and I know that the 4S group are already investigating some of the points that you raise. Let us see, for example, whether the benefit is related to initial cholesterol concentration. I am not persuaded that publication of your hypothesis would be helpful to readers at this stage.

Yours sincerely

Robin Fox

The correspondence mentioned in Dr. Fox's letter indeed produced results. Four years later a new 4S report was published, and in that paper the authors claimed the presence of exposure-response. However, the finding concerned only the first year of the trial.[\[189\]](#) In a letter in *Läkartidningen*, the Journal of the Swedish Medical Association, I asked one of the authors, Professor Anders G. Olsson, to explain why they had published the exposure-response calculations for the first year, but not for the whole trial,

in which, according to the presentations at the meetings in Sweden, there was no exposure-response. Olsson answered with the following words:

“Anyone obsessed by a particular idea is able to draw cocksure conclusions from selected subgroup analyses.”

I still wonder to whom Olsson referred.

There is strong evidence for alternative, so-called pleiotropic effects of the statins, which I pointed out in my rejected manuscript and also in a subsequent letter to *The Lancet*,[\[190\]](#) and the following year other researchers also published similar ideas.[\[191\]](#)

The statins inhibit the body’s production of a substance called mevalonate, which is an early precursor to cholesterol, but also to many other substances with biological importance. The way the statins interfere in mevalonate metabolism is therefore complex and difficult to predict, like guessing what will happen if a hammer is thrown into a complicated machine. It is possible to draw a few conclusions, however.

Reduced amounts of mevalonate may explain why statin treatment has anti-inflammatory effects,[\[192\]](#) makes smooth muscle cells less active[\[193\]](#) and platelets less inclined to produce thromboxane.[\[194\]](#) One of the first steps in the process of atherosclerosis is the growth and migration of smooth muscle cells inside the artery walls, and thromboxane is a substance that is necessary for blood clotting. By blocking the function of smooth muscle cells and platelets, statin treatment may provide benefit for cardiovascular disease by at least two mechanisms, both of which are independent of cholesterol levels.

The protective effects of simvastatin were demonstrated in heart transplantation studies in rats.[\[195\]](#) Normally, the function of transplanted hearts gradually deteriorates because the coronary vessels are narrowed by an increased growth of smooth muscle cells in the vascular walls. This condition is called graft vessel disease, a condition with many similarities to early atherosclerosis. However, rats that received simvastatin had considerably less graft vessel disease than control rats that did not receive simvastatin, and this was not due to cholesterol reduction because simvastatin does not lower cholesterol in rats. In fact, LDL-cholesterol was highest in the rats receiving simvastatin.

In another experiment a flexible collar was placed around an artery in rabbits.[196] After two weeks the arteries with collars became narrow, but less so if the rabbits had received simvastatin. Again, the effect had no relation to the rabbits's cholesterol levels.

Thus, the statins in some way protect against cardiovascular disease, but their effect is not due to cholesterol reduction. The proponents of the cholesterol hypothesis have simply had incredible luck in finding a substance that prevents cardiovascular disease and at the same time lowers cholesterol. The question is, however, whether the benefits would have been even better if the statins didn't lower cholesterol.

But why bother about mechanisms? Isn't it wonderful that the statins work? Shouldn't we all take statins?

The costs

To answer that question it is necessary to look at the figures from the trials. Take a look at the figures for "number of heart disease deaths, relative risk reduction," in Table 7A. You will find that coronary mortality in these trials was lowered between 19 percent and 41 percent, most in the 4S trial and least in the CARE trial. These are the so-called relative risk figures that are used by the trial directors and by the drug companies in their ads. But let us also look at the absolute figures, the "absolute risk reduction," on the next line. Here you will find that death from a heart attack was prevented in only a small percentage of the treated individuals. This figure was highest in the trials that included patients with heart disease, whereas it was a trivial 0.12 percent in the AFCAPS/TexCAPS trial, which included healthy individuals with normal cholesterol.

Table 7A. Summary of the outcome of the first six statin trials.

| m = men,women Ctr: Control group; NS: Not significant. *: p = 0.05; **: p = 0.01; ***:p = 0.001 | | | | | | |
|---|------------|-----------------|-------------|-----------------|--------------------|-----------------|
| Trial | EXCEL | 4S | WOSCOP S | CARE | AFCAPS/TexCA PS | LIPID |
| Drug | Lovastatin | Simvastati n | Pravastatin | Pravastati n | Lovastatin | Pravastati n |

| | | | | | | |
|-------------------------------|--------------------------------------|--|--------------------------------------|--|--|---|
| Length of trial; years | ? | 5.4 years | 4.4 years | 5 years | 5.2 years | 6.1 years |
| Type of participants | Healthy people with high cholesterol | Patients with CHD and high cholesterol | Healthy people with high cholesterol | Patients with CHD and normal cholesterol | Healthy people with normal cholesterol | Patients with CHD and all levels of cholesterol |
| Number of participants | | | | | | |
| in drug/control group | 6600/1650 | 2221/2223 | 3302/3293 | 2081/2078 | 3304/3301 | 4512/4502 |
| Percent male: | 59 | 82 | 100 | 86 | 85 | 83 |
| Age | 18-70 | 35-70 | 45-64 | 21-75 | men 45-73 women 55-73 | 31-75 |
| Cholesterol at start | | | | | | |
| LDL, mean | 180 | 190 | 192 | 139 | 150 | 150 |
| LDL, range | - | - | >155 | 115-174 | 131-191 | - |
| Total cholesterol, mean | 258 mg/dl | 263 mg/dl | 272 mg/dl | 209 mg/dl | 221 mg/dl | 218 mg/dl |
| Total cholesterol, range | - | 215-312 mg/dl | >252 mg/dl | <240 mg/dl | 181-266 mg/dl | 155-271 mg/dl |
| Degree of lowering | | | | | | |
| LDL cholesterol | ? | 35% | 26% | 28% | 26% | 25% |
| Total cholesterol | ? | 25% | 20% | 20% | 19% | 18% |
| Total number of deaths | | | | | | |
| Drug/control group; numbers | ? | 182/256 | 106/135 | 180/196 | 80/77 | 498/633 |
| Percent | 0.5/0.2 | 8.2/11.5 | 3.2/4.1 | 8.6/9.4 | 2.4/2.3 | 11/14.1 |
| Relative risk | +150% | -29% | -21% | -8% | +3.9% | -21% |

| | | | | | | |
|---|-------------|-----------|---------|---------|----------------------|-------------|
| reduction; % | | | | | | |
| Absolute risk reduction; % | +0.3% | 3.3% | -0.9% | -0.77% | +0.09% | -3% |
| Statistical significance | ? | *** | NS | NS | NS | *** |
| Number of CHD deaths | | | | | | |
| Drug/control, group; numbers | ? | 111/189 | 38/52 | 96/119 | 11/15 | 287/373 |
| percent | ? | 5/8.5 | 1.2/1.6 | 4.6/5.7 | 0.33/0.45 | 6.4/8.3 |
| Relative risk reduction; % | ? | -41% | -27% | -19% | -27% | -23% |
| Absolute risk reduction; % | ? | -3.5% | -0.42% | -1.1% | -0.12% | -1.9% |
| Statistical significance | ? | *** | NS | NS | NS | *** |
| Number of nonfatal CHD | | | | | | |
| Drug/control group; numbers | ? | 353/502 | 143/204 | 135/173 | 116/183 ^a | 336/463 |
| Percent | ? | 15.9/22.6 | 4.3/6.2 | 6.5/8.3 | 3.5/5.5 | 7.4/10.3 |
| Relative risk reduction; % | ? | -30% | -22% | -22% | -38% | -27% |
| Absolute risk reduction; % | ? | -6.7% | -1.8% | -1.8% | -2% | -2.9% |
| Statistical significance | ? | *** | *** | * | *** | *** |
| Similar effects in both sexes | ? | No | - | yes | yes | yes |
| Effect in all age groups | ? | yes | yes | yes | yes | yes |
| Effect on other cardiovascular diseases | ? | yes | no | yes | - | yes |
| Effect independent | Not studied | yes | yes | yes | yes | Not studied |

| | | | | | | |
|---|--|--|--|--|--|--|
| of degree of cholesterol lowering | | | | | | |
|---|--|--|--|--|--|--|

Put another way, the chance of not dying from a heart attack over four to six years for a patient with heart disease and high cholesterol is about 92 percent without treatment, and increases to 93 or 94 percent if he takes a statin tablet every day.

For healthy individuals, the figures are even less impressive. In the WOSCOPS trial, for instance, the chance for a healthy man with high cholesterol of not dying from a heart attack during the five years of the study was 98.4 percent without treatment and 98.8 with treatment. In the AFCAPS/TexCAPS trial, the chance of surviving was 99.55 percent without treatment and 99.67 with treatment. Most likely, no effect was seen at all because such small differences may just as well be caused by chance.

Let us compare these figures with another kind of treatment, for instance, treatment of urinary tract infections. Nine out of ten women with a urinary tract infection will recover immediately if treated with an appropriate antibiotic for a few days, at the cost of a few dollars. But in the 4S trial, for instance, they treated 28 patients for five years to prevent one fatal heart attack; in the other secondary prevention trials, they treated at least twice as many to achieve the same result. So, while one of the patients benefited from the treatment, the others took the drug in vain because they would have survived anyway.

The costs for the drug alone amounts to about \$150,000 per saved life, but that was in 1994, the year for the publication of the first statin trial; to-day it is much cheaper. In the trials, all expenses are paid by the drug companies, but in real life, the patient or society must pay, not only for the costs of the drug but also for the doctors' fees, laboratory analyses and loss of income during the doctor visits. And to prevent one fatal heart attack in healthy people, if it is possible at all, 235 individuals with high cholesterol and 826 individuals with normal cholesterol have to consume a statin drug for four to five years.

Of course, there may be other gains. Not only did statin treatment prevent coronary death, it also prevented more than twice as many nonfatal heart

attacks. We should also subtract the costs for hospital care and other treatments for the patients whose heart attacks we prevent, not to mention the grief and pain associated with the loss of wives or husbands or close friends. In the most optimistic calculations, the costs to save one year of life in patients with heart disease have been estimated to be about \$10,000; much more for healthy individuals.

This may not sound unreasonable. Isn't a human life worth \$10,000 or more?

The implication of such reasoning is that in order to add a few more years of life for a few people, more than half of mankind should take statin drugs every day from an early age to the end of life. It is easy to calculate that the costs for such treatment would consume most of any government's health budget. And if this kind of money is spent to prolong the life of a few healthy individuals with statin treatment, what will remain for the care of those who really need it? Shouldn't health care be given primarily to the sick and the crippled?

But what is even worse, those who recommend statin treatment for healthy people ignore the fact that the treatment may produce disease instead of preventing it.

The side effects

Drugs that interfere with normal bodily functions usually have unexpected and unintended effects and so is the case with the statins. According to the drug producers and the trial directors, adverse effects from statin treatment are rare and mild, as indeed they should be, because they are aimed at life-long treatment for millions and millions of patients and healthy people. And the drug companies are of course eager to tell us that they are harmless considering the huge income they have already generated. According to Marcia Angell, former editor-in-chief of The New England Journal of Medicine, the combined profit for the ten drug companies on the magazine Fortune's list of the world's 500 most profitable companies was higher than the profit of all the other 490 put together.[\[197\]](#) And the statins are by far the most prescribed drugs today. In 2002, for instance, the income to Pfizer for atorvastatin was \$9 billion in the US alone. Evidently, as Dr. Angell

says, the drug companies' aim is "to load the dice to make sure their drugs look good." And they are clever enough to do so.

Myopathy and rhabdomyolysis

Statins block an enzyme called hydroxymethylglutaryl coenzyme A reductase, an enzyme that is necessary to produce mevalonate, and mevalonate is the building block not only for cholesterol, but also for a substance called coenzyme Q10, or simply Q10. This substance is located to the mitochondria of our cells, and the mitochondria is the cell's power plant. No energy is produced without this vital molecule and its importance is particularly great where energy is needed the most, in the muscle cells. And muscle complaints are also the most frequently reported side effect from statin treatment.

Authors of the statin trial reports claim that muscle complaints, or myopathy, occur in less than 1 percent of patients, but this is with all certainty an underestimation. Other authors, independent of the drug companies, have found much higher frequencies. Thus, a research group lead by Helmut Sinzinger at the University of Vienna found that muscular side effects are seen in about 25% in patients who do regular exercise. They also studied this problem in 22 professional athletes with familial hypercholesterolemia who were treated with various statins. Sixteen, or three out of four, discontinued the treatment because of muscle side effects. [198] Competitive athletes may be more sensitive to muscle pain and muscle weakness than the rest of us, but even mild symptoms may have a deleterious effect on elderly people who already have muscular weakness. And considering that the best, the cheapest and the least risky way to prevent heart disease is regular exercise, muscular problems may directly counteract any possible benefit achieved by statin treatment.

Now compare these figures with those given in table 6A. Whereas at least 20 percent suffered from muscular problems, only a few percent gained benefit from statin treatment.

When muscles are damaged, the concentration of an enzyme called creatine kinase, or CK, becomes elevated in the blood. Elevated CK is thus an early sign of muscle damage, both of the skeletal muscles and the heart. We are told that elevated CK is seen in less than one percent of patients treated with

statins as well. But trial directors insist on a CK elevation ten times higher than the normal upper limit and taken at two successive determinations before they call it elevated.

Similarly, liver damage, another side effect, is only reported if the liver enzymes in the blood are more than three times higher than the normal upper limit, and again, only if it has been reported twice.

I have never heard or read about anyone questioning this practice. No one seems to be asking what happens to the liver after ten or twenty years of statin treatment in those whose liver enzymes are only 2.5 times higher. And what happens to the muscles of those whose CK is only nine times higher?

The habit of diagnosing muscle damage only if CK is elevated, whether just a little or quite a lot, is also questionable, because microscopic examinations of muscle tissue from statin-treated patients have shown signs of damage in patients with a normal CK.[\[199\]](#) And even patients on statin treatment, but without muscular symptoms, may be damaged. In a study of muscle tissue using electron microscopy, the structural integrity of skeletal muscle fibres was compromised in 10 of 14 statin-treated patients without any subjective complaints, but in only one of eight control individuals.[\[200\]](#)

In rare cases, myopathy progresses to the destruction of muscle tissue, a condition called rhabdomyolysis. Large amounts of a muscle protein called myoglobin are liberated into the blood, and too much myoglobin in the blood clogs the kidneys leading to renal failure. A few years after the introduction of Bayer's statin drug Baycol, fifty patients receiving Baycol were reported to have died from renal failure, and Bayer was therefore forced to withdraw the drug from the market. According to a more recent report from Bayer, more than 100 patients had died from kidney failure. The number of patients who needed dialysis or a kidney transplant as a result of Baycol treatment is unknown. This number must be much higher because to-day treatment of end-stage renal failure is highly effective, in particular in young and middle-age people.

Rhabdomyolysis is seen after treatment with other statins also, but less frequently. In a recent review of statin side effects the authors found 4.4 cases of rhabdomyolysis per 100 000 patient years after pravastatin,

simvastatin and atorvastatin treatment. But there is obviously something wrong with such figures. In the TNT trial (see later), where statin doses up to eight times higher than normal were used, five non-fatal cases of rhabdomyolysis were reported, four of them during the treatment period. However, the authors claimed, that these cases had nothing to do with the treatment because they were not dose-dependent.

But if the four cases observed in the TNT trial were not due to treatment, and if the figure for rhabdomyolysis mentioned above is true, it means that rhabdomyolysis should be twice as common in untreated people as in those treated with statins. This is obviously not true. Rhabdomyolysis is rarely seen spontaneously; it always occurs secondarily to something else, for instance severe muscle injuries as a result of arterial occlusion or deep venous thrombosis in the legs, or to exposure to toxic chemicals or drugs. The odds are that arterial thrombosis may have been the cause in one of the cases. But even so it is highly unlikely that none of the cases were associated with statin treatment. Obviously, trial directors try to cover up the truth about statin side effects. And this is only part of the evidence.

Heart failure

The heart is also a muscle and therefore should be affected by a decrease in Q10. As early as 1990, the biochemist Karl Folkers, who first described the molecular structure of Q10, reported that lovastatin lowered the concentration of Q10. What he also found was that the function of the heart went downhill whereas Q10 treatment was able to improve it.[\[201\]](#) Several recent trials have confirmed the beneficial effect of Q10 treatment in patients with heart failure.[\[202\]](#)

Heart failure is not reported as a side effect of statin treatment according to the trial reports, probably because patients with heart failure are routinely excluded from statin trials, but also because heart failure may be seen as the result of the primary disease rather than an adverse effect. This is most likely what the practicing doctor will think as well, because heart failure is not mentioned as a potential side effect on the drug labels.

Brain problems

Apart from the adrenal glands, the highest cholesterol concentration is present in the brain. The brain cells themselves produce practically all of

this cholesterol because in the brain, little or no LDL-cholesterol is taken up from the blood. The rate of cholesterol synthesis is extremely high in the central nervous system of the fetus and the newborn, probably explaining the severe malformations and dysfunctions of the brain seen in children with Smith-Lemli-Opitz syndrome, an inborn error of cholesterol metabolism that leads to extremely low cholesterol values. Cholesterol is used as a component in the membranes of the brain cells and the nerve fibres and is also vital for proper function of the synapses, the connections between the nerve cells. It is therefore not too farfetched to assume that low cholesterol levels may adversely affect brain function in normal people. Indeed, we have much evidence to support this idea.

In several of the trials a larger number of the treated individuals died from violence or suicide. In none of them was the difference statistically significant, but all studies pointed in the same direction. Most diet-heart proponents belittle this problem. It must be coincidental, they say. It is out of the question to conclude that lowering cholesterol makes people more likely to die from violence or suicide.

Matthew Muldoon and his team from the University of Pittsburgh, Pennsylvania, were the first to point out this phenomenon.[\[203\]](#) Their conclusion was that if all the trial results were added up in a meta-analysis, the increased number who died from violence and suicide was, in fact, statistically significant. Fewer died from a heart attack, but more from violent and sudden deaths. The authors also stressed that low blood cholesterol levels are seen more often in criminals, in people with diagnoses of violent or aggressive-conduct disorders, in homicidal offenders with histories of violence and suicide attempts related to alcohol, and in people with poorly internalized social norms and low self-control.

In a comment on the paper, David Horrobin, the editor of *Medical Hypotheses*, wrote that the most serious consequence of cholesterol-lowering measures is invisible. If low cholesterol levels cause violence and depression, then intervention to reduce cholesterol on a large scale could lead to a general shift to more violent patterns of behavior. Most of this increased violence would not result in death but in more aggression at work and in the family, more child abuse, more wife-beating and generally more

unhappiness. Such events are not recorded in the trials—no one asks about them—and they are therefore never detected.[\[204\]](#)

In other words, we are told about the number surviving a heart attack, but not about the number surviving violence or suicide attempts.

The conclusions of Muldoon and co-workers were strengthened by a large investigation in Sweden by Dr. Gunnar Lindberg and his team. They measured cholesterol in more than 50,000 men and women and kept track of them for 20 years. During the first six years, five times more had committed suicide among those with low cholesterol compared with those whose cholesterol was high.[\[205\]](#)

The increased risk of suicide disappeared with time. The authors therefore concluded that the increased risk may be associated with a concentration of cholesterol below a subject's habitual value, which means that the risk of suicide is greater if low cholesterol is induced by diet or drugs.

Several others have confirmed the association between low cholesterol and depression, suicide and suicidal attempts.[\[206\]](#) Not unexpectedly, relapse in cocaine addiction is also seen more often in people with low cholesterol,[\[207\]](#) and cholesterol levels in monkeys, dogs, and human beings with a violent behavior patterns fall most often in the lower end of the scale.[\[208\]](#)

Beatrice Golomb, a professor of medicine at the University of California in San Diego, has devoted much of her research on the side effects of statins and she is today the most knowledgeable researcher in this area. In a meticulous analysis of all studies published since 1965 that looked at the association between low or lowered cholesterol levels and violence, she concluded that the association is causal, and that the risk of creating violent behavior should be taken into consideration before doctors advise their patients cholesterol lowering measures.[\[209\]](#) Together with her co-workers she reported about patients with severe irritability and short temper on statin treatment. All of them recovered after discontinuation. A strong argument for a causal role of the statin treatment is that re-challenge with the drug in four of the patients led to reappearance of their anti-social behavior.[\[210\]](#)

There is no medical term for irritability and shortness of temper, so therefore the statin trials do not record these changes in behavior. As far as the trial directors are concerned, these effects are not on their radar screen.

But they are in full view of the family members and friends who must cope with the personality changes in the patient taking statins, as well as hugely present with the patients themselves, whose golden years may suddenly become overcast with a bleak and grumpy outlook on world... all for the presumed benefit of adding a few months of life to the human carcass.

Progressive dementia in two patients on atorvastatin was described by Dr. Deborah King at the University of Mississippi. After discontinuation of the drug a dramatic improvement was observed in both patients.[\[211\]](#)

Leslie Wagstaff, and his team at Duke University searched the FDA's MedWatch surveillance system for reports of statin-associated memory loss and found 60 cases. The symptoms varied between short-term memory loss, and total amnesia. Usually the symptoms appeared after several months of treatment and disappeared after its withdrawal.[\[212\]](#)

The influence of cholesterol on memory was studied in hundreds of women by Professor V. W. Henderson and his team at the University of Arkansas. They found that LDL-cholesterol, but no other lipids, was strongly associated with the memory score, just as was the case in Professor Muldoon's study. Women with high cholesterol scored better than women with medium cholesterol, and women with medium cholesterol scored better than women with low cholesterol. They also compared the score with changes in LDL-cholesterol levels over several years and found that women whose cholesterol increased had a better score than women whose cholesterol went down.[\[213\]](#)

Memory loss, or amnesia is a common and entertaining theme in the movies. In real life it is very rare, at least before the statins were introduced. One of the victims of this scary condition was Dr. Duane Graveline, astronaut, aerospace medical researcher, flight surgeon and family doctor. In his book *Lipitor, Thief of Memory*, Graveline described how he himself became a victim of temporary but total memory loss.

Six weeks after his annual astronaut physical, where he had been prescribed Lipitor because of high cholesterol, he was found by his wife aimlessly walking around close to their home. He didn't recognize her and refused to go into their house, and it took her much time and persuasion before he, utterly reluctantly, got into their car so they could go to their family doctor.

He was finally examined by a neurologist who, after a thorough examination couldn't find anything wrong except for the amnesia. No recommendations were given and shortly after the examination he felt completely normal. Eventually, however, Graveline began suspecting that the cause of the amnesia might have been his treatment with Lipitor and he therefore stopped taking it.

At the next physical Dr. Graveline was again prescribed Lipitor. Neither the NASA doctors, nor any of the many doctors or pharmacists whom he had consulted, had ever heard about this side effect, so he followed their advice. Six weeks later he experienced a second episode of amnesia that lasted for twelve hours. This time he couldn't recall anything that had happened after high school. His years on college, his training at medical school, his time as a USAF flight surgeon, his marriage and his four children, his selection by NASA as a scientist astronaut, his twenty years as a family doctor, his busy retirement and his eight books, all of it had disappeared, and also all that he had learned. Afterwards he realized that he would not even have been able to treat a common cold.

Again, everyone denied any possibility of a Lipitor association. But this time Dr. Graveline himself was convinced that the drug was the villain. He wrote a letter about his experience that was published in the nationally syndicated column, *The People's Pharmacy*.

Graveline was referred to a statin drug study at UCSD College of Medicine, where the principal investigator, Dr. Beatrice Golomb told him that she knew of several similar cases, and after publication of his letter, hundreds of distraught patients and relatives and even a few doctors contacted him. They told about a full array of cognitive side effects, from amnesia and severe memory loss to confusion and disorientation, and all of them were associated with statin treatment.

Similar stories are still reported to and filed by the Federal Drug Administration. However, to date the agency has taken no action—not even issued a warning. “The subject is still being reviewed,” was their most recent response according to Dr. Graveline, if they bothered to reply at all.

Anyone who has been prescribed a statin drug is urged to read his book and its follow-up, *Statin Drugs Side Effects and The Misguided War on*

Cholesterol, or at least go to his website, where he summarizes what he has learned from thousands of victims who have contacted him after the publication of his first book. Here are his words about amnesia:

“For every reported case of transient global amnesia there are hundreds of case reports of impaired memory, disorientation and confusion among an older group of patients that rarely, if ever, get mentioned. All too frequently, this group is willing to accept old age, ‘senior moments’ or incipient senility as the cause, particularly when their physicians are also ignorant about this side effect.”

Meanwhile, pilots taking statins still fly planes, truck drivers taking statins still drive trucks and parents and grandparents taking statins still drive their children and grandchildren in cars. Is anyone safe with such a large proportion of the population on statins?

Peripheral polyneuropathy

If low cholesterol is bad for the brain, it is reasonable to assume that it is bad for the peripheral nerves also. A reasonable guess and, unfortunately, it seems to be true. Damage to the peripheral nerves is called polyneuropathy. This is a most disturbing and painful condition that starts in the feet and legs and may spread to other parts of the body. Pain, burning, tingling and even total loss of sensation are common symptoms. Polyneuropathy may lead to muscular weakness and difficulty walking as well.

In Denmark all residents have a civil registration number that is used in discharge prescription registries, so that it is possible to find all residents with a particular disorder and find out which drugs they have been taking. In one of Denmark's counties with a population of 465,000, Dr. David Gaist and his team at Odense University Hospital asked all patients who had polyneuropathy of unknown cause to see how many were on statin treatment compared with the general population in the county. They calculated that the risk for definite polyneuropathy was 16 times higher for statin users than for non-users, and even higher for those who had used statins for more than two years.[\[214\]](#)

The authors stressed that the frequency of polyneuropathy was very small, but they also pointed out that it increased over time. The question is, of course, how many statin-treated individuals may have polyneuropathy after

20 or 30 years of treatment? Nobody knows. The problem is particularly serious for patients with diabetes, because even without statin treatment diabetics run a much greater risk to develop polyneuropathy than other people. Polyneuropathy in statin users has been seen by other researchers as well. For example, Elias Ragi, consultant clinical neurophysiologist at Royal Devon and Exeter Hospital, Exeter, reported about 16 patients with statin-induced polyneuropathy in just one year, and many of them had severe symptoms.[\[215\]](#)

Impotency

There are many reports about erectile dysfunction after statin treatment. To get an impression of its frequency, Dr. Anthony Wierbicki and his team at St. Thomas Hospital, London asked 82 patients who were going to start on statin therapy about their sexual functions. Six months later 20% of the patients had become more or less impotent.[\[216\]](#)

Again, drug labels provide no mention of this embarrassing side effect, and from my clinical experience I know that few men would dream of bringing it up with their doctors.

It is also worth mentioning that Dr Wierbicki's study was sponsored by Pfizer. However, nothing is mentioned about this potential side effect on the official Lipitor site. And why should they? Just take a Viagra pill, another bestseller from Pfizer.

Worse than thalidomide

On the drug labels pregnant women are warned against statin treatment. But how many read the fine print? Furthermore, about half of all pregnancies are unplanned, and any adverse effects on the fetus occur already within the first two months.

To learn more about these effects, Drs. Robin Edison and Maximilian Muenke at the National Institutes of Health reviewed 178 cases of statin exposure reported to the FDA. After having excluded those with spontaneous and voluntary abortions they ended up with 52 cases considered valuable. Almost half of them had serious malformations of the brain or the limbs.[\[217\]](#)

But that is not all. At the Oncogenetic Laboratory of the Tel Aviv University, Dr. Tartakover-Matalon and his team studied living placental tissue retrieved from normal pregnancies that had been terminated legally. They found that if they added small doses of simvastatin to the culture medium, several vital functions of the placental cells were inhibited. They concluded that these toxic effects might have caused the higher abortion rate and malformations seen in previous studies of animals given statins during pregnancy.[\[218\]](#)

There is reason to believe that the many cases of spontaneous abortions reported by Drs. Edison and Muenke also were caused by the statins.

Cancer

Statins produce cancer. This was the conclusion of University of California researchers Thomas Newman and Stephen Hulley after having analysed all studies of what happened when laboratory animals were treated with statins.[\[219\]](#)

They asked themselves why these drugs had been approved by the Food and Drug Administration at all. The answer was that the doses used in the animal experiments were much higher than those recommended for clinical use. But as Newman and Hulley commented, it is more relevant to compare blood levels of the drug. Their review showed that the blood levels that caused cancer in rodents were close to those seen in patients on statin drugs.

Because the latent period between exposure to a carcinogen and the incidence of clinical cancer in humans may be 10 to 20 years or more, the absence of any controlled trials of this duration means that we do not know whether statin treatment will lead to an increased rate of cancer in coming decades. Thus, millions of healthy people are being treated with medications the ultimate effects of which are not yet known. Newman and Hulley therefore recommended that the statins should be used only for patients at very high risk for coronary disease, not for people with life expectancies of more than ten years. Healthy people with high cholesterol as their only risk factor belong to the latter category. Yet these are the very people targeted for cholesterol-lowering drugs in the current trend toward mass medication. There is good reason to exercise caution in the use of the

statin drugs because there is already much evidence that statin treatment may lead to cancer in humans as well.[\[220\]](#)

If statin treatment is cancer-provoking, cancer is likely to show up first in people with the highest risk of cancer, for instance in old people. There are also great differences between the incubation period for different cancers. Those that appear the earliest are, of course, those that are easy to detect. The results from the statin trials are therefore disquieting.

In the first two simvastatin trials, 4S and HPS, more patients in the treatment group got non-melanoma skin cancer. However, although these figures appeared in the tables, the authors did not mention this alarming finding in the discussion or in the summary of the reports. The reason may be that the difference was not significant in each trial. However, if the numbers from both trials are added together, the difference becomes statistically significant, meaning that it is highly unlikely that the result was due to chance.

Non-melanoma skin cancer is considered unimportant because it is easy to treat; nobody dies from non-melanoma skin cancer today. However, a cancer is a cancer. If statin treatment or low cholesterol are able to create various types of cancer as in the animal experiments, the first type we should expect to see is, of course, skin cancer, simply because it is easily detected and at an early stage. Besides, there is evidence that non-melanoma skin cancer may be a harbinger of more vicious types of cancers later on.[\[221\]](#) But by unknown reasons the trial directors of all studies published after HPS haven't bothered to report the number of skin cancers.

No significant increase of cancer was seen in a ten-year follow-up of the participants in the 4S trial and the authors therefore concluded that ten years of statin treatment does not induce cancer.

Neither does ten years smoking.

Another easily detectable malignancy is breast cancer. In the CARE study, breast cancer was more common among those who took the drug than in the control group. In the treatment group 12 women got breast cancer during the trial, whereas there was only one case in the control group, a difference that is highly statistically significant.

The authors of the CARE report were eager to explain away the increased frequency of breast cancer. “These findings could be an anomaly,” they wrote. It is possible that they are right because the expected number of breast cancer cases in the control group, calculated from the frequency normally seen in the population, should have been five cases. Nevertheless, thirteen is more than twice as many as five.

Breast cancer has not been reported in any of the more recent trials, but after the publication of the CARE trial, all patients with cancer, including those who have undergone cancer treatment, have been excluded from the trials. This is a most curious decision because supporters of statin treatment claim that statins are able to prevent cancer.

In the package insert for Pravachol, you can read about the risk of various less dangerous side effects, although none of these was reported significantly more often in the treatment group. But nothing is mentioned about the possible risk of breast cancer, the only side effect that was seen significantly more often.

And there is more evidence that statin treatment may cause cancer. Let us take a look at PROSPER, a large trial involving elderly people.[\[222\]](#) This trial was directed by Professor James Shepherd, the director of the WOSCOPS trial. In PROSPER, men and women aged 70-82 were included only. All of them had either vascular disease or had a raised risk of such disease. At follow-up, 4.2 percent had died from a heart attack in the control group, but only 3.3 percent in the treatment group. This small benefit was neutralized by a higher risk of dying from cancer. Indeed, there were 28 fewer deaths from heart disease in the pravastatin group, but 24 more deaths from cancer. If we include non-fatal cancer in the calculation, the cancer difference between the two groups became statistically significant; 199 in the control group and 245 in the pravastatin group. Furthermore the difference between the two groups increased year for year.

To put this finding in context, as they wrote, they counted the number of new cancers in all pravastatin trials together and found that there was no significant increase of cancer. However, in this calculation they did not include the number of skin cancers.

What they also forgot to mention was that in the previous trials the participants were 20-25 year younger than in their own trial. Cancer is primarily a disease of old age and cancer is a frequent finding at post-mortem of old people who have died from something else. Cancer in the elderly is often dormant or it grows so slowly that it never becomes a problem during their lifetime—unless of course the growth is stimulated by something like statin treatment.

If cancer appears within a mere three or four years in the elderly, isn't it likely that cancer will become a problem in young people, those who have been told to take a statin drug every day the rest of their life?

There is another way to determine whether statin treatment is able to produce cancer. At five hospitals in Tokyo a group of Japanese researchers studied whether cancer patients had been treated with statins more often than other people. To that end they selected patients with various forms of lymphoid cancers and control individuals of the same age and sex without cancer admitted to other departments at the same hospitals during the same period. A total of 13.3 percent of the cancer patients, but only 7.3 percent of the control individuals were or had been on statin treatment.[\[223\]](#) Again, just as with skin and breast cancer, lymphoid cancer is easily detectable, at least compared with cancers in the internal organs. Had the Japanese researchers chosen patients with pancreatic cancers for instance they might not have found any difference, because this cancer type may go undetected for many years.

Effect and side effect

As you can see from Table 6C, the gain in the number of fatal heart attacks in the CARE trial was 1.1 percent whereas the loss in numbers of breast cancers was 4.2 percent. Calculated in the way trial directors usually do, as relative rather than absolute risk, the difference was even more striking, with 12 percent fewer heart attacks but 1500 percent more breast cancers. However, you will never see side effects calculated in this way—only positive effects. (Unfortunately, the authors did not give the number of fatal heart attacks for each sex. The figures in the table relate to both sexes.)

How to minimize side effects

Patients chosen for the statin trials do not look like the typical patient sitting in the doctor's waiting room. To be included they must satisfy a long list of criteria. As an example I shall tell about how the participants were selected for the TNT trial, but the principles used in that trial are similar to those of the others.[\[224\]](#)

At the start, the researchers screened 18,469 patients with evident coronary heart disease. Of these, 15,464 were deemed eligible. We are not told why the other 3,005 patients were not eligible, but from the many previous trials we know that patients with all kinds of pre-existent conditions or frailty are disqualified. As mentioned above, cancer is one of the exclusion criteria, but any serious condition, such as kidney and liver disease, heart failure, uncontrolled diabetes, hormonal dysfunction, and gastrointestinal disorders belong to that category—including, of course, any patient who has previously shown intolerance to statin therapy.

After that the 15,464 potential participants were given a small dose of atorvastatin, the drug to be tested. This procedure led to the exclusion of a further 5,462 patients. According to the authors, most of them were excluded because they did not meet the randomization criteria, a most curious argument as these criteria were already defined from the beginning. Why weren't they excluded in the first round? Others were excluded because they experienced adverse effects from atorvastatin, or they died, or had a vascular event during the test, or they showed lack of compliance.

Thus, from the original group of 18,469 patients only 10,001 patients, or 54 percent were included in the trial. It is obvious that the participants in the trial represented a selection of unusually strong and healthy patients. Taken together with the unwillingness to record obvious signs of organ dysfunction as side effects, the figures for statin side effects are obviously completely unreliable.

Another note of caution

To test a drug on many thousands of patients is extremely costly and laborious. The only groups willing to spend several hundred million dollars for such trials are the drug companies because the potential profit is gigantic. Consequently, all statin trials are sponsored by the company whose drug is tested in the trial. Not only do the companies pay for the necessary

meetings, workshops, conferences, authors' and speakers' fees and travel expenses for the many hundreds of participating doctors and researchers in each trial, they also prepare the trial, take part in the selection of patients and control individuals, design and produce the protocols, participate in monitoring of the results, analyze blood cholesterol and are responsible for the complicated statistical calculations. The companies may even hire professional writers to prepare the reports. Can we be totally confident that their vested interests have no influence at all on the outcome of these trials? Can the wolf play the role of shepherd?

And are the results really blinded as we are told? In most of the trials the lipid analyses are performed at the drug company laboratories, and these results are not released to the doctors and patients throughout the whole trial. But what about the lipid analyses that were performed at the individual clinics and departments—were they blinded also? When the first favorable results from the trial are announced in the press, for example, how do you think the participants would react? Wouldn't they want to know whether they were taking the new wonder drug or whether they were taking an ineffective placebo? An easy way to find out is to take a cholesterol test. Almost certainly, all of them knew their cholesterol level at the beginning of the trial. A new cholesterol test would in most cases have told them to which group they belonged, and even if their trial doctor hadn't analyzed their cholesterol, it would have been easy to have it done somewhere else.

So it is not unreasonable to assume that a substantial proportion of the patients and their doctors knew to which group the participant belonged and such information might have unintentionally influenced the results.

But let us assume that the doctors and the patients were not influenced at all. What about the trial directors? By now you are familiar with the tendency of the previous directors to exaggerate the trivial effects of their treatment and minimize the side effects. In fact, many of these reports do not appear to have been written by scientists in search of the truth and nothing but the truth.

Consider also that positive results are much more financially rewarding for researchers than negative ones. Researchers, who come up with positive results, in particular positive results from drug trials, are more often invited

as speakers to meetings and congresses and more often chosen for further lucrative research projects.

Should we, therefore, be confident that statin research results have been presented in a nonpartisan manner? And why haven't we heard about the outcome of the first statin trial, the EXCEL study?

EXCEL, the Expanded Clinical Evaluation of Lovastatin

This trial was performed by Dr. Reagan H. Bradford and his team from a large number of American clinics and research institutions, including the Merck Sharp & Dohme Research Laboratories at West Point, NY, where the drug was produced where the drug was produced. More than 8,000 healthy individuals (called "patients" in the trial reports) with cholesterol levels between 240 and 300 mg/dl (6.2-7.7 mmol/l) received one of four different doses of lovastatin (Mevacor®) or a placebo.[\[225\]](#)

With a view to reporting on possible adverse effects of the treatment, preliminary study results were published after only one year of the trial. No significant side effects were reported, but in the fine print the authors were obliged to mention that death due to all causes was 0.5 percent in the four lovastatin groups combined (32 or 33 individuals out of a group of about 6,600—no exact figures were given in the report) compared to 0.2 percent in the placebo group (three or four individuals out of a group of 1,650). By taking all the lovastatin groups together, the difference would have been statistically significant if the number of deaths in the treatment groups were 33, but not if it were 32. Even if the difference wasn't statistically significant after one year, it would certainly have become significant if the tendency to a higher mortality in the treatment groups had continued throughout the trial. In any case, the aim of the treatment was to lower mortality and most certainly no lowering was achieved.

Today at least 20 reports from the EXCEL trial have been published in various medical journals. These reports tell us how well lovastatin is tolerated and how effective it is in lowering blood cholesterol levels in various populations, but not one of them has reported the final outcome of the trial, although more than ten years have passed since it began. Therefore, we do not know whether the increased mortality, seen after just one year of treatment, has continued throughout the trial.

Why have we never heard about this outcome of the first statin trial, which was one of the largest? I asked that question in a letter to Merck, Sharp & Dohme. They answered that, “the trial was not designed to measure the clinical outcome, only to test whether the drug was tolerable and did not produce any serious side effects.”

New guidelines

On May 16, 2001, an expert panel from the National Cholesterol Education Program published new guidelines for “the detection, evaluation and treatment of high blood cholesterol.”[\[226\]](#) The guidelines introduced new risk factors that demand preventive measures (or “risk-reduction therapy,” as they call it) and widened the limits for the old ones.

The main target is LDL-cholesterol, they said, because “*research from experimental animals, laboratory investigations, epidemiology and genetic forms of hypercholesterolemia indicate that elevated LDL-cholesterol is a major cause of heart disease.*” (If you have read this book from the beginning you will probably agree with me that such research has indicated nothing of the kind.) The optimal values should be 150 mg/dl (3.8 mmol/l) for LDL and 200 mg/dl (6.1 mmol/l) for total cholesterol. But if there were any risk factors present, the optimal cholesterol level should be even lower. The more risk factors, the lower cholesterol should be.

In the highest risk category were patients with heart disease because, according to the statistics from Framingham, they run a more than 20 percent risk of having a new heart attack in ten years. (The report did not tell us where to find these figures, however.) Other atherosclerotic diseases were said to be just as risky, such as is diabetes from the age of twenty. And the presence of two or more other serious risk factors was said to put the patient at a similar risk.

The new guidelines provided an intricate scoring system showing how the different risk factors were graded. Men with an accumulated score of 15 or more belonged to the highest risk category. And it was easy to get a high score. For instance, if you were seventy years old, you were automatically given 12 points. A cholesterol level above 275 mg/dl (7.05 mmol/l) at age 39 gave you 11 points, less with increasing age. An untreated systolic blood

pressure reading of 130 mm Hg (which is completely normal) got one point, two if you were on antihypertensive treatment.

Smokers below age 40 got eight points, and you are a smoker if you have smoked at least one cigarette during the previous month. Women needed a higher score to be placed in the highest risk category, but they got more points for their risk factors.

The guidelines recommended that everybody over age 20 had his or her cholesterol level tested every fifth year. If you were in the highest risk category and your LDL-cholesterol was above 100 mg/dl (2.6 mmol/l), you should change your life habits; if your LDL was above 130 mg/dl, (3.3 mmol/l) you should immediately start cholesterol-lowering treatment. But you might as well start with both measures, said the guidelines, because few people succeeded in lowering their cholesterol by life-habit intervention alone—although in another place in the paper the authors claimed that life-habit intervention was an effective way of lowering cholesterol!

Emerging risk factors

The indications for treatment were stronger if there were other risk factors than those mentioned above, for instance if you were overweight, if you exercised too little or if you ate too much animal fat. Even “emerging” risk factors should be taken into consideration, and by emerging risk factors the authors included almost all laboratory tests that, on average, had been found higher in patients with heart disease. According to the authors, “the emerging risk factors do not categorically modify LDL-cholesterol goals; however, they appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy.” (In other words, take a bunch of laboratory tests and most of us become candidates for statin treatment.)

Subclinical atherosclerosis

One of the emerging risk factors was called “subclinical atherosclerotic disease.” The guidelines gave no explanation for this new concept. The term comes from a new technique called electron beam tomography that is a method for depicting calcifications without putting a catheter up into the coronary arteries. The degree of calcification is said to reflect the degree of atherosclerosis and is therefore a much better predictor of future heart

attack than high blood cholesterol or, for that matter, any other risk factor. According to an advertisement for one of those huge health centers that have become popular in the US, *“The electron beam tomography scan gives individuals who have risk factors for heart disease a painless, non-invasive way to obtain peace of mind knowing that early indications of heart disease are or are not present.”*

Whether you obtain peace of mind is questionable because in the most recent study using electron beam tomography, sixty percent of a group of healthy women over age 55 had “subclinical atherosclerosis,” yet, according to the new guidelines, half of these women belonged to the low-risk category.[\[227\]](#) In other words, with one blow this new technique has landed many further millions of healthy people into the high-risk category.

The most surprising finding, at least for those who have not read this book, was the lack of an association between degree of calcification and total or LDL-cholesterol or any other lipid fraction. The authors of the study had no comments about this finding—which of course is totally devastating to the cholesterol hypothesis—except to say that they considered the new guidelines insufficient and suggested regular electron beam tomography for the whole population. I sent a short letter to William W. Parmley, the editor of the journal (*JAMA*) where I told about the many other studies with similar results and asked him, why the authors did not question the cholesterol hypothesis. He answered: “Because of space limitations we are able to publish only a few letters addressing controversial issues.”

More new risk factors

The guidelines stated officially for the first time that high triglycerides should be lowered and low HDL-cholesterol should be raised. True enough, admitted the authors, no study has proven that raising HDL-cholesterol provides any benefit. (There is no evidence that lowering triglycerides provides any benefit either.) Nevertheless, they recommend treatment with clofibrate (Atromid-S® Abitrate®) or nicotinic acid (niacin®). Obviously, the many unsuccessful trials with these drugs and their many harmful side effects had been completely forgotten.

As an argument for using cholesterol-lowering drugs, the supporters claim that 20 percent of patients with coronary heart disease have a heart attack

within ten years. But that number is obtained by including minor symptoms without any clinical significance. Many people survive even a major heart attack with few or no symptoms after recovery.

Heart attacks may even appear without any symptoms. I have seen many patients myself with indisputable ECG indications of a recent myocardial infarction, but who recall no more than slight discomfort, if any symptoms at all, during the preceding weeks. What matters is how many die and this is much less than 20 percent.

Lower and lower

New guidelines have appeared regularly for at least 40 years. In 2004, new trials inspired the National Heart, Lung, and Blood Institute to publish a set of updated guidelines, according to which, cholesterol should be lowered even more aggressively than before.[\[228\]](#) This advice was based on three trials.

In two of them, REVERSAL[\[229\]](#) and PROVE-IT,[\[230\]](#) half of the patients were treated with 40 mg pravastatin, half with 80 mg atorvastatin. The “best” effect was seen in the high-dose groups, where LDL-cholesterol was lowered by 46 and 51 percent respectively, whereas in the pravastatin groups it was lowered by 25 and 22 percent respectively. Therefore, the authors argued that we should take cholesterol down to much lower levels than previously recommended. They also considered their result as proof of exposure-response.

But you cannot study exposure-response with two different drugs, because there are large differences between the other, the so-called pleiotropic effects of the various statins. Furthermore, the eight times higher dose of atorvastatin (the usual dose is 10 mg) only cut cholesterol marginally more than the usual dose. In a previous atorvastatin trial named ASCOT for instance, 10 mg atorvastatin lowered LDL-cholesterol by 35 percent whereas the eight-times-higher dose in the two trials mentioned above lowered it only by a further 12 percent and 16 percent respectively.

In a third trial, named TNT (Treatment to New Targets),[\[231\]](#) about 10,000 patients with stable heart disease were treated with atorvastatin for five years; half of them with 10 mg and half with 80 mg. Again, the “best” effect was seen after 80 mg and the authors claimed that their study was a

further support to the new guidelines. Some curious things emerged from that trial, however.

First, total mortality was almost identical in the two groups; 5.6 percent in the low-dose group, 5.7 percent in the high-dose group. The reason was that the fewer who died from cardiovascular disease was outnumbered by a larger number dying from other causes. These causes were not given, however, and our request for more details was ignored.[\[232\]](#)

Second, heart mortality was significantly lower in the high-dose group, but the report only provided the number of “non-procedure-related myocardial infarctions.” By non-procedure-related infarctions is meant heart attacks that have not occurred during operations or diagnostic investigations at the hospital. The latter infarctions should, of course, have been included as they have been in all other trials. There can only be one explanation why the researchers have omitted them—their number was higher in the high-dose group. Had more occurred in the low-dose group, the authors with all certainty would have reported them.

Benefits and risks

The fact that the number of side effects was larger than the number of patients that benefited from treatment should have given the authors great concern, all of whom have strong financial ties to Pfizer, the sponsor of the trial. If doctors recommend a high statin dose to their patients, they should be able to tell them whether the benefit of such treatment counterbalance possible harmful side effects, but no such useful information emerges from this trial report.

Patients with non-fatal cardiovascular diseases such as a myocardial infarction and stroke often recover completely. It is therefore not self-evident that the many side effects are balanced by the lower incidence of cardiovascular events. A relevant question to a patient with heart disease is whether he prefers memory loss (which with all certainty was not regarded as a side effect, as nothing about that is mentioned anywhere in the official reports or on the drug labels) instead of a non-fatal heart attack, which often heals without serious sequels. Or ask whether he prefers polyneuropathy, which may become permanent as an invalidating and very unpleasant condition, or a minor stroke, which may heal without any sequels.

An alarming report

After the publication of the new guidelines, yet another trial comparing normal and high-dose was published, the IDEAL trial.[\[233\]](#) In this trial, where usual-dose simvastatin was compared with 80 mg atorvastatin, no significant difference was seen either as regards the major endpoints. Even worse, the number of adverse effects was far higher. Almost 90 percent had side effects and almost half of these were recorded as serious. No, this isn't a printing error: almost half of them!

The authors did not comment on this alarming finding except by mentioning that, "there was no difference between the groups in the frequency of adverse events that were rated as serious." Nor did they inform the reader about the nature of these events. In their answer to our request[\[234\]](#) the authors responded as follows:

"The numbers do not represent only drug-related adverse effects. In accordance with good clinical trial practice, the study protocol required that all observed or volunteered adverse events, whether or not considered drug-related, should be recorded during the trial. This included worsening or increase in severity or frequency of preexisting conditions as well as minor and serious new signs, symptoms, or laboratory findings. In a population of middle-aged or elderly coronary disease patients aged up to 80 years, it is rare that anyone does not have at least an episode of common cold or a minor musculoskeletal injury over a period of 5 years. The frequency of all adverse events in the IDEAL study was therefore as expected. Adverse events considered definitely or possibly drug-related were few, and significant differences between the two treatment groups were presented in the article. The frequency was not greater than in comparable trials."[\[235\]](#)

How could the authors know whether the frequency of all adverse events was "as expected?" The number of common colds and minor injuries has never been reported in any previous trial; neither can they be classified as serious. And why didn't they tell us about which adverse effects they considered drug-related?

The large number of side effects may have another explanation. As mentioned above, almost half of the patients originally selected for the TNT

trial were excluded because of various types of weaknesses or diseases or because they didn't tolerate the drug. In the IDEAL trial, only eight percent were excluded. These patients may therefore have been more similar to patients in real life, and many of the "new signs, symptoms, or laboratory findings" may have been due to the drugs.

Why are trial directors always so eager to sweep all disadvantageous observations under the rug? Aren't they concerned about future patients? Shouldn't they follow the words of Hippocrates: *"First, do no harm."*

Is the explanation to be found at the end of their letter, which states as follows:

"Financial Disclosures: Dr. Pedersen has reported receiving consultation fees and speaker's honoraria from Pfizer, Merck, Merck AG, and AstraZeneca and research grants and steering committee fees from Pfizer and Merck. Dr. Kastelein has reported receiving research grants from Pfizer. Drs. Olsson and Holme have reported receiving honoraria from Pfizer as steering committee members. Dr. Bendiksen was previously employed by Pfizer Norway and has reported receiving honoraria from Pfizer as a steering committee member."

Can we trust the drug companies?

In his book "The Whistleblower," Peter Rost, a former top executive in Pfizer, reveals a company riddled with corruption. According to Rost, Pfizer and other drug companies spend huge amounts of money to promote their trials. One way is to pay renowned researchers for putting their name on the final trial report, when, in fact, the reports are written by PR firms. Also, according to Richard Smith, former editor at the British Medical Journal, many medical journals are packed with articles ghostwritten by pharmaceutical companies.[\[236\]](#)

The FDA recently cited Pfizer for publishing the results of a Valdecoxib trial in a manner that obscured the risks and the drug now has a black box warning. Pfizer has also pleaded guilty to numerous charges of false advertisements and agreed to pay billions of dollars to satisfy criminal and civil penalties. Pfizer funded the TNT trial, paid its directors and authors, analyzed the data, and assigned one of their employees as co-author of the

trial report. There were thus numerous opportunities to have influenced the results, knowingly or unknowingly.

The new guidelines may possibly prevent cardiovascular death in a small minority of patients with cardiovascular disease. But at the same time they may increase mortality from other diseases, transform healthy individuals into unhappy hypochondriacs obsessed with the chemical composition of their food and their blood, reduce the income of ranchers and dairy farmers, undermine the art of cuisine, destroy the joy of eating, and divert health care money from the sick and the poor to the rich and the healthy. The only winners are the drug companies and imitation food industry—and the researchers that they support.

And there are more problems with the advice we receive from the authorities. Read on!

False safety

Many side effects from new drugs do not appear before they are used in greater scale. Doctors are told to report all new, unexpected side effects, but there is a great risk that they are underreported. Most drugs have side effects either because they are toxic or because the patient is hypersensitive to the drug. Therefore, the side effects appear very soon after the start of the treatment and the patient therefore easily recognize the symptoms as a result of the treatment. The statins are not directly toxic and they do not result in hypersensitivity reactions. The statins disturb the normal synthesis of several important substances in our body. It may therefore take a long time before these substances are totally depleted and symptoms of deficiency appear. Both the patient and the doctor may therefore overlook that late symptoms may be caused by the drug. Statins are used mostly in old people. Cancer, loss of memory, weak muscles, impotency and heart failure are common in old people and may therefore be considered as natural effects of old age. Furthermore, old people are often treated with many different drugs. In Sweden, for example, old people discharged from a medical or cardiology department are often prescribed a dozen or more different drugs. So, even if doctors should suspect that the patient's symptom were caused by the medicine, how can someone determine which of the medicines is to blame?

That side effects are underreported is obvious from a study in Rhode Island, USA. A questionnaire sent to all practicing doctors and answered by 74% showed that the serious side effects reported to the FDA during the previous year corresponded to only one percent of the numbers actually seen.[\[237\]](#)

It is comforting to learn that many patients realize themselves that the statins are toxic. In Ontario, Canada researchers studied how many people had continued their statin treatment. A total of more than 140,000 old people were included in the investigation. Two years after the first statin prescription two thirds of those who already had a heart disease, and three fourth of those whose only “disease” was high cholesterol had discontinued.[\[238\]](#)

The alleged omnipotence of statin drugs

You may probably have read in the newspapers about the many other allegedly positive effects of the wonder drugs, the cholesterol-lowering statins. Carefully placed articles now claim that statins can prevent cancer, ankylosing spondylitis, chronic obstructive pulmonary disease, severe sepsis, heart failure, hip fractures, and much more. The way the researchers have studied these allegedly beneficial effects is confounded with a serious bias, however. As an example I shall analyse one of these claims, the idea that statin treatment prevents Alzheimer’s disease.

First, studies claiming that statin treatment is good for almost any disease do not come from trials where the control individuals have cholesterol levels just as high as those in the treatment group. Instead, comparisons are made between people treated with statins and control people selected from the same community, but who are not treated with statins.

Obviously these people’s cholesterol is lower than those treated with statins, at least lower than their cholesterol before treatment, which means that the researchers have compared the outcome of low-cholesterol people with high-cholesterol people, and there are many studies showing that people with high cholesterol are healthier in many aspects compared to people with low cholesterol.

For starters, most studies have found that old people with high cholesterol live longer than old people with low cholesterol. But we have also some specific data about brain function and cholesterol. For instance, Bianca

Schalk and her team at the University Medical Center in Amsterdam, Holland followed more than 1,000 people age 55-85 for three years and found that those whose cholesterol was lower than 200 mg/dl (5.1 mmol/l) were more likely to decline in functional performance tests such as walking, turning around, dressing themselves and standing up and down from a kitchen chair with folded arms.[\[239\]](#)

Another Dutch study showed that among more than 6,000 people above age 55 and followed for nine years, women with high cholesterol developed Parkinson's disease less often than women with low cholesterol; the higher the cholesterol, the lower was the risk.[\[240\]](#)

Researchers at the Johns Hopkins University, Baltimore and Göteborgs University, Sweden followed 382 old people for ten years. Among those with the highest cholesterol values much fewer had dementia at follow-up than the others.[\[241\]](#) In accordance with these findings is a study from the Framingham Heart study. Here Penelope Elias and her team followed about 2,000 individuals for 16-18 years. A detailed record of their ability to learn, to reason, to concentrate and to organize showed that there was a direct association with these mental performances and cholesterol; the higher cholesterol, the smarter they were.[\[242\]](#)

Let us have a look at Alzheimer's disease itself. The allegation that low cholesterol prevents Alzheimer comes from comparisons between people on statin treatment and people who are not, and obviously there are unavoidable errors associated with such a comparison. A better way to get an answer is to compare initial cholesterol in people who develop Alzheimer and in those who do not. This was done by Dr. G. Li and others at the University of Washington, Seattle. After five to six years, about 13% of more than 2000 old people had developed Alzheimer's disease or all-cause dementia and on average, their cholesterol did not differ from the others.[\[243\]](#)

People who take lipid-lowering agents might also be wealthier than those who do not, because statin treatment is expensive and wealthy people are healthier than poor people. The only way to decide whether statin treatment prevents Alzheimer's or any other disease is a controlled clinical trial. Let us see what they have to tell us about this subject.

The protocol for PROSPER, the trial where old people were treated with pravastatin (Pravachol), included psychometric tests and a mental examination every year. At the end of the study, the directors concluded that their mental functions declined at the same rate in the treatment as in the control group. Similar findings were reported in the WOSCOPS trial. Thus, no evidence either that the statins other effects are able to prevent Alzheimer.

To study the effect of cholesterol lowering on memory, Professor Matthew F. Muldoon assigned 192 healthy adults to a six-month double-blind trial. Half of the participants were treated with Lovastatin and half of them with placebo. At the start and at the end of the trial a large number of tests were performed to assess neuropsychological performance, depression, hostility and quality of life.[\[244\]](#)

Normally, when such tests are performed repeatedly, the test subjects improve because of learning or practice, and this was indeed seen in the control group. But tests of attention and psychomotor speed, which are not subject to this type of error, gave significantly lower scores in the Lovastatin group. The change in performance was unrelated to the percent change in LDL-cholesterol but was significantly related to the level achieved after treatment with Lovastatin; the lower the cholesterol, the worse was the memory.

Thus, the claim that statin treatment or low cholesterol levels protect against Alzheimer's disease has no scientific basis; if anything these results rather suggest the opposite.

Those who pay

Financial disclosures for the authors of the NCEP guidelines 2004 were not given in the original publication. After a critical letter from Merrill Goozner of Center for Science in the Public Interest (CSPI) who questioned the scientific basis and objectivity of the guidelines, the financial disclosures were published on the web:

Financial Disclosure[\[245\]](#)

Dr Grundy has received honoraria from Merck, Pfizer, Sankyo, Bayer, and Bristol-Myers Squibb.

Dr Hunninghake has current grants from Merck, Pfizer, Kos Pharmaceuticals, Schering Plough, Wyeth Ayerst, Sankyo, Bayer, AstraZeneca, Bristol-Myers Squibb, and G. D. Searle; he has also received consulting honoraria from Merck, Pfizer, Kos Pharmaceuticals, Sankyo, AstraZeneca, and Bayer.

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Myth 8: Polyunsaturated Oils are Good for You

Intervening is a way of causing trouble.

Lewis Thomas

Risk at both ends of the scale

The smaller number of heart deaths in the soybean trial of Dr. Dayton and his team, mentioned in chapter 6, was offset by a larger number of cancer deaths. Does it mean that soybean oil causes cancer?

Diet-heart proponents would argue that Dr. Dayton's soybean trial was an anomaly, and that other trials with polyunsaturated fat have not resulted in more cancer. However, never before had such huge amounts of polyunsaturated fat been eaten over such a long period of time. Dr. Dayton's patients were also much older than in the other trials, and thus more susceptible to cancer, which means that a possible cancer-provoking effect could be detected more easily.

Another disquieting fact is that many studies have reported a low cholesterol to be a risk factor for cancer. The purpose of these studies was to follow a great number of individuals for many years to see if the Framingham researchers were right when they claimed that high cholesterol means a high risk of a heart attack. Surprisingly, these more recent studies revealed that it was just as dangerous to have a very low cholesterol level, as it was to have a very high one. Those who had very low cholesterol levels had a greater incidence of cancer while those with very high cholesterol suffered more heart attacks.

Most investigators thought that low cholesterol levels were not the cause but the *result* of the cancer since cancer cells need cholesterol, just as any other cells do. Perhaps their rapid growth and greater need for cholesterol reduced the cholesterol levels in the blood?

It is interesting that the diet-heart proponents immediately relegate low cholesterol to a secondary and thus an innocent phenomenon in the etiology of cancer, but never admit that *high* cholesterol might be a secondary and thus innocent phenomenon in the etiology of heart disease. No, say the diet-

heart proponents, high cholesterol is always dangerous and should be lowered by any means.

A great number of studies also found that cholesterol was low many years before the cancer was discovered. [246] If the low cholesterol was a consequence of rapid cancer growth, then the level should decrease when the cancer started to grow. But in some patients cholesterol was low eighteen years before the cancer appeared.

Of course, this fact was a serious drawback for those who planned cholesterol-lowering measures of most of the population, and the diet-heart proponents therefore met in 1981 to discuss the problem.[247]

The meeting was of sufficient importance to attract most of the leading American cholesterol researchers, including Jeremiah Stamler, director of two major cholesterol-lowering trials and author of a large number of papers that expanded on the dangers of high cholesterol; Basil Rifkind, head of the Lipid Metabolism Branch at the National Heart, Lung and Blood Institute, and later head of the LRC trial; Robert Levy from Columbia University, chairman of the meeting and previously director of The National Heart, Lung, and Blood Institute; Antonio Gotto, director of the American Heart Association; Ancel Keys, and many more of those who made up the anti-cholesterol army.

Predictably, the participants concluded that low cholesterol did not cause cancer, but they were unable to explain the phenomenon. It was a subject for future research, they noted, but not a threat to public health.

The published report from the meeting stated: *“It was an unanimous opinion of the panelists that the data did not preclude, countermand, or contradict the current public health message which recommends that those with elevated cholesterol levels seek to lower them. There is evidence of a possible increase in cancer risk at very low cholesterol levels (but) the risk is generally modest.”*[248]

These were their words. By “very low levels” the panel meant less than 4.7 mmol/l (183 mg/dl). But diet-heart proponents do not consider 4.7 mmol/l (183 mg/dl) too low when it comes to treatment of *high* cholesterol. A couple of years later for instance members of the National Heart, Lung, and Blood Institute and the American Heart Association (many of whom

participated in the meeting) recommended that people should bring their cholesterol levels down to at least 4.85 mmol/l (188 mg/dl).

It is not certain that low cholesterol levels provoke cancer: the fact that cancer is seen more often in individuals with low cholesterol is no proof of cause and effect. Low cholesterol level is a *risk factor* for cancer, precisely as high cholesterol is a risk factor for heart disease.

Again, a risk factor is not necessarily the cause. Something may produce cancer and at the same time lower blood cholesterol. Chemical compounds with such a potential do exist.

Burglars among molecules

“Somewhere, on some remote planet... on the other side of our galaxy, there is at this moment a committee nearing the end of a year-long study of our own tiny, provincial solar system. The intelligent beings of that place are putting their signatures... to a paper, which asserts, with finality, that life is out of the question here and the place is not worth an expedition. Their instruments have detected the presence of that most lethal of all gases, oxygen, and that is the end of that.”

With these words Lewis Thomas, the famous essayist and professor of medicine opened one of his speeches to his new students. Thomas's story is not pure fantasy—oxygen can be dangerous.

A civil war rages inside us from the sweet second of fecundation until we end as dust or ashes. Atoms and molecules are fighting for the tiny elements that are surrounding them, the electrons. The haze of electrons gives identity and character to each atom and molecule; if the number of electrons is altered, a valuable molecular citizen may, in a split second, be turned into a useless and even destructive hoodlum.

Electrons prefer to be present as couples. Paired electrons furnish the atom or molecule with stability and resistance against harassment, but some pairs are more stable than others.

The main part of a fatty acids is composed of a core of carbon atoms to which hydrogen atoms are attached. When the number of hydrogen atoms is optimal their electrons form stable pairs with those of the carbon atoms. Examples of stable molecules are the saturated fatty acids, those said to be

dangerous to the heart and the vessels. They are called saturated because they are saturated with hydrogen.

Unsaturated fatty acids are short of hydrogen atoms. Monounsaturated fatty acids are missing two, polyunsaturated fatty acids are missing four or more. This means that instead of sharing one pair of electrons with each other, some of the carbon atoms are sharing two pairs of electrons with his neighbor carbon instead of one pair, forming the so-called double bond.

A double bond is less stable than a single bond. The hydrogen sitting close to the double bond is easily snatched by a free radical, a process called oxidation. Free radicals snatch hydrogen atoms because one or more of their electrons lack their partner; they are unpaired.

Combustion fumes, such as cigarette smoke and diesel exhaust, are especially rich in free radicals, but even the oxygen molecule is a free radical. It is especially active when heated. If the temperature is high enough, all its neighbors are oxidized—they burn. But what we are interested in here is oxidation at body temperature.

Inside the cells of our body oxidation is vital to cell function and life as long as this process is controlled by hormones and enzymes. Step by step sugar and other fuel molecules are oxidized to water and carbon dioxide, a process that releases energy for the cell machinery. So far, so good.

But if oxidation occurs without control, as it may do if we are exposed to free radicals, molecules other than sugar may be oxidized. Among these others are the unstable polyunsaturated fatty acids. Loss of hydrogen atoms is disastrous to a polyunsaturated fatty acid (as to other molecules as well), because its stability is ruined and it is split into lesser molecules with nasty qualities.

Usually the human body is protected against oxidation thanks to many various antioxidants, kind molecules that donate hydrogen atoms to the free radicals thus protecting us against uncontrolled oxidation. Vitamin E, for example, is a well-known and important antioxidant that protects the polyunsaturated fatty acids in our cell membranes. There are many others.

But if too many polyunsaturated fatty acids are present, or if too many free radicals are available, or if the amount of antioxidants is insufficient, then

protection from the antioxidants may fail.

Nobody knows the limit between harmless and harmful amounts of polyunsaturated fatty acids. Cholesterol campaigners now recommend no more than 10 percent of our calories from polyunsaturated oils, but give no reasons for the limit. They don't tell us about the evidence that an excess of dietary polyunsaturated fatty acids may be dangerous.

Does polyunsaturated oil produce cancer?

When too much polyunsaturated oil is given to laboratory animals their white blood cells are damaged so that the animals die more easily from infectious diseases and cancer. We do not know for sure whether the same is valid for human beings, but we do know that our immune system is sensitive to a surplus of polyunsaturated fatty acids. If a preparation of such oils is added to the diet of patients who have received a kidney graft the function of their white blood cells is hampered resulting in a better acceptance of foreign material, including the transplanted kidney.[\[249\]](#)

But other foreign and less useful material, such as bacteria and virus, may be accepted also. One of the great problems with transplant patients is that their immunosuppressive treatment makes them more vulnerable to infection. It is a general rule that any substance which harms the white blood cells also stimulates infections. Some of these substances may even stimulate cancer.

It has never been proved that polyunsaturated fatty acids stimulate cancer, but proof may come in time. By analogy, cigarette smoke may produce cancer, but only after many years of exposure.

Do polyunsaturated oils make you age faster?

It is commonly accepted that aging is partly a result of the eternal fight of free radicals for electrons. If laboratory animals are exposed to free radicals, or to substances highly sensitive to free radicals—if, for instance, these animals eat great amounts of polyunsaturated oils—yellowish pigments are stored in many organs. The same pigments develop in most creatures including man, and accumulates with age.

The fact that polyunsaturated oils may accelerate aging was demonstrated by Dr. Edward Pinckney. In collaboration with a plastic surgeon he asked a

large number of patients how much polyunsaturated oil they usually consumed.

Fifty-four percent of the patients said that they had increased their intake considerably. Of those patients 78 percent showed marked clinical signs of premature aging, and 60 percent had required the removal of one or more skin lesions because of suspected malignancy. Of the patients who had made no special efforts to consume polyunsaturated oils the figures were 18 and 8 percent respectively.[\[250\]](#)

Today most deep-frying is done in vegetable oils. Very few know that if polyunsaturated oils are kept hot over many hours, its ability to produce cancer in laboratory animals increases.[\[251\]](#)

Do polyunsaturated oils make you stupid?

Polyunsaturates have other nasty effects. Premature children have only small amounts of vitamin E in their bodies. Dr. Joshua Ritchie and his team in San Francisco studied seven premature babies who were admitted to the hospital with widespread edema, anemia, disturbances of the blood cells and lack of vitamin E. The researchers found that the most plausible cause was the food; these children had all received commercial formulas composed of skim milk and vegetable oils with a high content of polyunsaturated fatty acids.[\[252\]](#)

The brain has low levels of vitamin E. This fact may explain why chickens fed polyunsaturated fat develop brain damage very quickly.[\[253\]](#)

Do polyunsaturated oils cause atherosclerosis?

A new theory about the origin of atherosclerosis is that it is not normal cholesterol, but oxidized cholesterol that is dangerous.[\[254\]](#) And oxidized cholesterol means cholesterol that has been damaged by free radicals.

Even in the fetus the walls of the arteries are speckled with fat. The microscope shows that these speckles or fatty streaks are composed of white blood cells filled with tiny bubbles. These cells are called foam cells. But the substance is not foam; it is cholesterol.

Patients with homozygous familial hypercholesterolemia have foam cells also. This fact was a stumbling block to the Nobel prize winners Michael

Brown and Joseph Goldstein. What they discovered was that in individuals with the rare genetic error called familial hypercholesterolemia, cholesterol molecules in the blood do not enter the cells as they do in normal individuals. The reason is that their key to the cell, the so-called LDL-receptor, is defective. Individuals who have inherited the disease from one parent (heterozygous form) have too few receptors; those who have inherited the disease from both parents (homozygous form) have no receptors at all. The lack of LDL-receptors explains why patients with familial hypercholesterolemia have a high blood cholesterol level.

But how can cholesterol enter the foam cells in patients with the homozygous form of familial hypercholesterolemia if, as Brown and Goldstein suggested, the cholesterol door to the cell is closed? This is certainly a crucial question because diet-heart proponents consider these foam cells the forerunner of atherosclerosis.

Recent studies have shown that it is not normal cholesterol which accumulates in the foam cells. Instead, it is oxidized cholesterol. And oxidized cholesterol has no problem entering the cells; it takes another route. The problem seemed solved. But how has cholesterol been oxidized?

There is much evidence that free radicals are the cause of the oxidation, and the source of free radicals is most probably the polyunsaturated fatty acids. For example, scientists can reduce the fatty streaks (called *atherosclerosis* by the proponents) in rabbits with familial hypercholesterolemia^[255] (named Watanabe rabbits) with the drug probucol, without lowering blood cholesterol.^[256] The explanation may be that probucol, just like vitamin E, is an antioxidant that hampers the attacks of free radicals.

On the other hand, lowering cholesterol in Watanabe rabbits does not reduce the fatty streaks.^[257]

If polyunsaturated fatty acids promote oxidation of cholesterol and thus atherosclerosis we should avoid eating too much of them. But diet-heart proponents continue to insist that it is more important to lower cholesterol by avoiding saturated fat and continue to recommend polyunsaturates as a substitute.

It is difficult to follow the proponents line of thought. The depositing of cholesterol in the artery walls of Watanabe rabbits was not reduced by

lowering the blood cholesterol but by preventing its oxidation. Then, does it make sense to lower cholesterol with polyunsaturated oils if too much of it stimulates oxidation?

One of the scientists introducing the new theory about oxidized cholesterol is Dr. Daniel Steinberg, from the University of California in La Jolla. He was the chairman of the consensus committee that started the American cholesterol campaign. This campaign has recommended that all Americans eat polyunsaturated vegetable oils instead of saturated fat. The committee recommended an upper limit of 10% for the consumption of polyunsaturated oil (now the reader know why). However, the committee did not call attention to the fact that the food they had previously called a protection against atherosclerosis was now seen as its cause.

It has not been proved, however, that oxidized cholesterol is the forerunner of atherosclerosis. A link is missing.

What has been demonstrated is that oxidized cholesterol is accumulated as fatty streaks, but the presence of fatty streaks is not the same as atherosclerosis. And the accumulation of cholesterol in fatty streaks has been shown in Watanabe rabbits, not in common rabbits. Because Watanabe rabbits inherit the same defect in cholesterol metabolism as people with familial hypercholesterolemia, the correct conclusion from the rabbit experiments is perhaps that fatty streaks in individuals with familial hypercholesterolemia may be induced by oxidized cholesterol.

However, there are observations that do suggest an adverse effect of polyunsaturated oil. In the worldwide epidemiological study of atherosclerosis the investigators found a connection between the degree of atherosclerosis and the total intake of fat. As there was no association between the intake of saturated fat and degree of atherosclerosis, the association obviously concerned unsaturated fats.

What we know for certain is that polyunsaturated fatty acids may produce a great many unfortunate things, none of them pleasant for human beings. We need polyunsaturated oils in small amounts to keep us healthy; some of them are even essential to life. Thanks to their lack of electrons, polyunsaturated fatty acids are soft and flexible. If our cell walls had only saturated fats, we would probably become as stiff as candles. But to have

too many polyunsaturated fatty acids is undesirable. After all, who would like his home to be occupied by terrorists?[258]

Trans fat

The fact that polyunsaturated fats such as corn, soybean, and sunflower oils are liquid, even at cold temperatures, has been a problem for the oil manufacturers in countries where butter and lard, not oil, are used in the diet. However, early in this century, French and German food technologists invented a method for converting vegetable oil into solid fat. They heated the oil to 150-200° Celsius in large reactors, mixed the oil with nickel powder that acted as a catalyst, and then forced hydrogen through this unappetizing soup. This method, still used today, changes the chemical structure of the polyunsaturated fatty acids and creates something called trans fatty acids. Trans fatty acids are also unsaturated, but the hydrogen molecules in the double bonds have been arranged so that the resulting molecules behave like the more solid saturated fatty acids. The final product, which is a mixture of various polyunsaturated, saturated, and trans fatty acids, is called partially hydrogenated oil and is used as an ingredient in many food products including margarine, crackers, cookies, doughnuts, french fries, potato chips, pastries and sweets.

Tiny amounts of certain trans fatty acids are also found in animal fats. However, the kinds of trans fatty acids that are produced by industrial hydrogenation have another chemical structure and are rarely found in natural food. By mistaking them for naturally occurring fatty acids, the human body may place them in the cell walls and other parts of human cells and because these trans fatty acids differ chemically there is a risk that we may suffer disturbances in cellular function if we eat too much of them.
[259]

Some fatty acids are vital just as vitamins are. This means that we cannot synthesize them ourselves, but need a small amount of them in our food. Normally, the risk is very small that we should suffer from lack of these fatty acids, because they are found naturally in most fats. However, when experimental animals are fed with trans fatty acids from hydrogenation, they develop symptoms similar to those that occur after a shortage of the vital fatty acids, either because the trans fatty acids are toxic by themselves or because they in some way inhibit the usage of the vital fatty acids. The

most serious effects concern reproduction. The testicles of rats are damaged, and the rats become sterile;[260] in mice, the fat content of the milk decreases.[261]

In human beings, trans fatty acids in the mother's blood pass over to the fetus. Whether it has any importance is uncertain, but a study by Dr. B. Koletzko at the Pediatric Department at Ludwig-Maximilians University in Munich on premature infants is suggestive. He found that a low birth weight in these children was associated with a higher proportion of trans fatty acids in the blood.[262] Of course, this is no proof that the low birth weight of these children was due to the excess of trans fatty acids, but the finding certainly gives rise to concern, because there is experimental evidence that trans fatty acids may inhibit growth, for instance from a study by Dr. Atal and his coworkers at various institutions at the University of Maryland and at the National Institutes of Health.[263] They gave young mice two different diets. The only difference between the diets was that a tiny amount of normal fatty acids (not of the vital ones) was substituted with the same amount of trans fatty acids. After two years the body weight of the mice fed with trans fatty acids was 20-25% lower than the weight of the control mice. Thus, although the mice had been given exactly the same amount of calories, those which ate trans fatty acids instead of other fatty acids did not grow as they should have done.

Too much dietary trans fat makes the blood cholesterol level rise.[264] Not that this effect matters in itself; if you haven't skipped Chapter 4 you may recall that atherosclerosis has nothing to do with the blood cholesterol level, and from Chapter 2 you may remember that most heart attacks are seen in people with normal cholesterol levels. But people who think that the cholesterol level is important should know, that by following the official recommendations and eating margarine rather than animal fats, they might raise their cholesterol instead of lowering it.

Trans fat is present in considerable amounts in solid margarine and in bakery shortenings. The consumption of trans fat has increased substantially in most Western countries during the last century. In the United States, it has increased from 12 grams per day and person before World War I to about 40 grams in 1985. This is the average figure; some people may eat more, especially if they have followed the recommendations of the National

Cholesterol Education Program, because very often fat that is called polyunsaturated on the food labels may be trans fat. Even the few people who prefer butter over margarine consume trans fat if they eat processed food products such as those mentioned above.

Many researchers, in particular those who advocate for the diet-heart idea, argue that the evidence is weak that trans fat is harmful to human beings. However, the mere suspicion that reproduction and growth may be hampered by an artificial nutrient, or that the same component may stimulate cancer growth, demands careful studies before it is distributed as food to most of mankind.

Dr. Ornish and The Lifestyle Heart trial

Coronary heart disease is a multifactorial disease that requires multifactorial intervention. This is the view of Dr. Dean Ornish and his group at the Preventive Medicine Research Institute, Sausalito, California, a view they share with many other doctors and researchers. Dr. Ornish and his group chose to intervene with a low-fat, low-cholesterol vegetarian diet, smoking cessation, stress-management training and moderate exercise. They selected 94 patients with a diagnosis of coronary artery disease according to a previous coronary angiogram. Fifty-three were randomly assigned to the experimental group and 43 to the control group, but when told about the design of the study only 28 and 20, respectively, agreed to participate.

A new angiogram was performed after one year, but one of the angiograms disappeared; in three patients the second angiogram could not be evaluated; one patient was not studied because of unpaid bills; one died during heavy exercise; and one dropped out because of alcohol misuse. Thus, only 22 patients in the experimental group and nineteen in the control group were available for analysis.

The result seemed promising. In the treatment group the total cholesterol fell by an average of 24 percent and LDL-cholesterol by 37 percent; mean body weight had decreased by ten kilograms; less severe chest pains were reported; and the coronary arteries had widened a little, whereas they had become a little more narrow in the control group. These improvements were strongly related to the degree of adherence to the intervention program in a “dose-response” manner, as the authors wrote in their report. The vascular improvements were still there after a prolongation of the study by five years, but now the difference was calculated using the less-demanding one-tailed t-test. Unfortunately, there was no difference in frequency, duration or severity of angina between the groups, but this unexpected finding was “*most likely*” due to bypass operations performed in the control group. Nothing was mentioned about how many operations had been performed, however, and no comparison was made between those who had not had an operation. In addition, a further six individuals were unavailable for follow-up study.

And there were more flaws. Not only was it an unblinded study, (although in the latest publication it was called blinded!), the low number of participants also resulted in a most uneven distribution of the risk factors. For instance, at the start the mean age was four years higher, mean total cholesterol 8 percent higher and mean LDL-cholesterol 10 percent higher in the control group; but mean body weight was almost 25 pounds higher in the treatment group. Such large differences between risk factors obviously complicate the evaluation of the treatment effect.

But let us assume that the improvement of the treated individuals was true and a result of the intervention—and this may well be possible—which of the intervention measures had a beneficial effect? Was it a weight reduction of more than 25 pounds? Was it a difference in smoking habits? (One in the experimental group smoked and stopped; nothing was mentioned about the number of smokers in the control group.) Was it the exercise? Was it the inner sense of peace and well-being produced by the stress-management education? Or was it a combination of these factors?

That the diet had any importance is unlikely because there is no evidence that vegetarians have a lower risk of coronary disease than other people. It is also unlikely that it was the change of LDL-cholesterol because at the end of the study there were no significant differences between these values in the two groups. The latter also contradicts the statement that the changes of coronary atherosclerosis and the diet were strongly correlated in a dose-response manner. To the pertinent question “*Precisely how strong were the correlations?*” asked by Elaine R. Monsen, editor of *Journal of the American Dietetic Association*, Dr. Ornish answered that *the study wasn’t really set up to do these kinds of analyses, so when we get beyond saying they’re correlated, we’re on shaky ground.*

It is laudable to try prevention without drugs, and we already know that it may be health-promoting to avoid being overweight, to exercise a little and to avoid smoking and mental stress, but with such weak evidence, why inflict a diet that only rabbits may find tolerable on millions of people? Perhaps the results would have been better if the patients inner sense of peace and well-being had been strengthened even further by allowing them to eat more satisfying and nutritious foods.

Ornish D and others. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. The Lancet 336, 129-133, 1990.

Ornish D. Reversing heart disease through diet, exercise and stress management: An interview with Dean Ornish. Journal of the American Dietetic Association 91, 162-165, 1991.

Gould KL, Ornish D and others. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. Journal of the American Medical Association 274, 894-901, 1995.

Myth 9: The Cholesterol Campaign is Based on Good Science

... the fourth and last wrong measure of probability I shall take notice of, and which keeps in ignorance or error more people than all the other together; is... the giving up our assent to the common received opinions, either of our friends or party, neighbourhood or country. How many men have no other ground for their tenets than the supposed honesty, or learning, or number of those of the same profession? As if honest or bookish men could not err, or truth were to be established by the vote of the multitude; yet this with most men serves the turn. If we could but see the secret motives that influenced the men of name and learning in the world, we should not always find that it was the embracing of truth for its own sake, that made them espouse the doctrines they owned, and maintained.

John Locke (1632-1704)

When two people share responsibility, they will each carry only one percent of the burden, at most.

Piet Hein

(1906-1996; Danish poet and physicist)

The proofs

“It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels...will reduce the risk of heart attacks caused by coronary heart disease.”

If you have read this book, you probably wonder if I just quoted a drug advertisement, and if the drug company got taken to court for misleading advertising practices. The statement, however, is quoted, word for word, from the summary of a consensus conference held at the National Institutes of Health in 1984[265]. The aim of this conference was to discuss how the results of the LRC trial should be translated into general recommendations for the American people.

The conference was headed by Basil Rifkind, who had been the director of the trial. Rifkind also determined who would be invited to join the panel that formulated the final recommendations.

Consensus is Latin for accord or unanimity. There were no such feelings in the audience, however. Among the many critical voices, Professor Michael Oliver from Scotland, the director of the early WHO trial, stressed that the trend towards an increased mortality from other causes was as strong as the trend towards a reduced mortality from coronary heart disease. “Why explain these results away?” he asked.

A British epidemiologist named Richard Peto admitted that in every trial “something ridiculous” had happened. But, he said, while no single trial was convincing, the trial evidence was impressive when analyzed together. (Does this sound familiar?).

Biostatistician Paul Meier from the University of Chicago opposed Rifkind's presentation of the LRC trial. He remarked: “To call ‘conclusive’ a study which showed no difference in total

mortality, and by the usual statistical criteria, an entirely non-significant difference in coronary incidents, seems to me a substantial misuse of the term."

There was no unanimity, either, about the treatment that was going to be introduced. One speaker at the conference advised lowering dietary cholesterol; another advised lowering dietary fat of animal origin and did not think that dietary cholesterol had any importance; a third member recommended lowering the caloric intake, no matter how.

The final statement from the conference resolved the disagreements by recommending all three dietary measures. Criticism from the audience was simply swept under the rug. Some of the critics were cut off by the panel chairman, Daniel Steinberg, who cited a lack of time. Requests to write a minority report were denied as inconsistent with the conference's goal of consensus.[\[266\]](#)

Let us now look at the findings, which the panel considered as the scientific support for their recommendations. Here they are at last, all the proofs, which, added to each other, supposedly speak overwhelmingly for the diet-heart idea. Knowing the radical measures, which followed, we can be confident that the panel members included all available arguments. Here they come, all the strong proofs.

Proof #1

The inherited disorders prove that high blood cholesterol by itself can induce coronary heart disease.

This is pure speculation. What we do know is that people with inherited disorders have high cholesterol because the passage of cholesterol from blood to cell is slowed down. What we also know is that atherosclerosis is more widespread and more severe in these individuals. But is it true atherosclerosis? And is it really caused by their high cholesterol?

What is special for individuals with familial hypercholesterolemia is best seen in the rare homozygous form, the form that appears when both parents have the deficient gene for the LDL-receptor. Autopsy studies of such individuals show that cholesterol deposition is increased, not only in their vessels, but generally, throughout their bodies. Many other organs are impregnated with cholesterol, just as is seen in cholesterol-fed rabbits.

The vascular changes seen in people with the more common heterozygous form of familial hypercholesterolemia are more difficult to analyze because these changes must partly be due to the metabolic error and partly to common atherosclerosis. And how do we know if possible effects of treatment stem from reduction of the changes caused by the inborn error or from reduction of atherosclerosis? Thus, any conclusion, which may be true for individuals with familial hypercholesterolemia, cannot possibly be valid for the rest of mankind.

Proof #2

Animals become atherosclerotic when they are fed diets that raise their blood cholesterol, and the atherosclerosis disappears when their cholesterol is lowered again with diet or drugs.

What the animal experiments are worth as evidence is seen in chapter 5. The fact that vascular changes, produced by an extremely unnatural diet, disappear when the diet is terminated cannot prove anything about human atherosclerosis. The fact that vascular changes produced by an extremely unnatural diet forced down in a stressed rabbit's stomach by catheter disappear when the diet is terminated cannot prove anything about human atherosclerosis. Weird John's gastric ulcer, caused by his swallowing iron nails, disappeared when John ceased eating hardware. But this is no proof that other patients' gastric ulcers are caused from eating building materials.

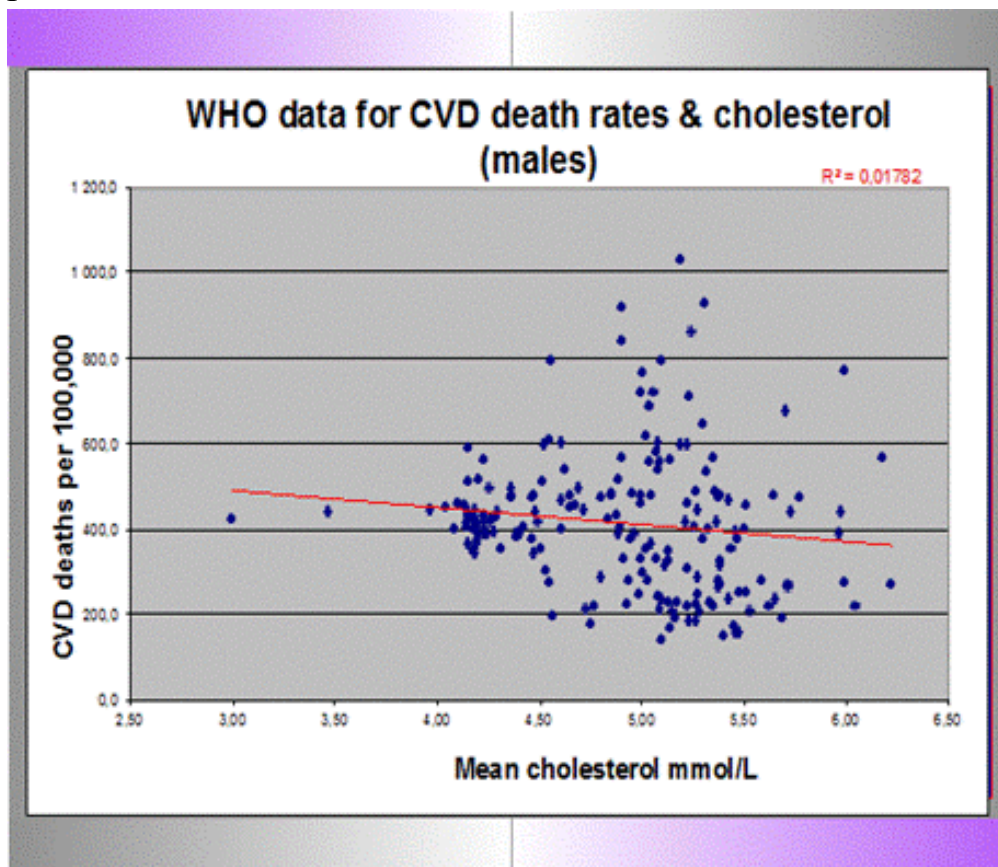
Wisely, nothing was said in the report about coronary heart disease, because it is not possible to produce this disease in animals only by increasing blood cholesterol.

Proof #3

There is a direct connection between blood cholesterol and the occurrence of coronary heart disease in various populations.

Look at this diagram. It is based on data from WHO and FAO and shows the association between cardiovascular mortality and serum cholesterol in various countries. If anything, low mortality is seen more often in countries where mean cholesterol is highest.

I



Proof #4

People who have emigrated to another country with a higher average blood cholesterol level gradually acquire the dietary habits, blood cholesterol concentrations, and CHD rates of their new country of residence.

The Masai people, the Polynesians and many more were ignored; nothing was said either about Marmot's studies of the Japanese emigrants.

Proof #5

Severity and frequency of raised plaques in the aorta and coronary arteries are strongly correlated with blood cholesterol levels.

Amazing, isn't it? Maintain any delusion again and again, no matter how far from reality it may be, and it may finally be taken for the truth. See chapter 5 for the facts.

Proof #6

Populations experiencing severe dietary (especially fat) limitations and weight loss have been shown to have less atherosclerosis and CHD and fewer heart attacks.

Many other factors than lack of dietary fat are different in severely deprived people; no conclusions can be drawn from such observations.

Proof #7

Epidemiological studies have shown that elevated blood cholesterol levels in healthy people predict the future occurrence of coronary heart disease.

... except for Maoris, Stockholmers, Greeks, Finns and Canadians, except for women and men after forty-seven, and except for those who already have had a coronary.

Proof #8

Evidence emerging from multiple clinical trials clearly indicates that lowering blood cholesterol levels in patients with a high blood cholesterol level decreases the likelihood of fatal and nonfatal coronary heart disease.

A few lines after the above statement, the consensus report said that none of the previous dietary trials had proven that a lowering of blood cholesterol can diminish the incidence of coronary heart disease. In both the "proving" trials (LRC and CLAS), cholesterol had been lowered with drugs because diet was considered insufficient. Thus, the panel admitted, that no trial with diet had proven beneficial. At that time no drug trial either had lowered fatal coronary heart disease with statistical significance.

Proof #9

Thus, the evidence obtained from genetic, experimental, epidemiological, and clinical intervention investigations overwhelmingly supports a causal relationship between blood cholesterol levels and coronary heart disease.

This was all of it. This is the scientific foundation of the cholesterol campaign, the numerous proofs that do not suffice one by one but that, taken together, are so “overwhelming.”

The panel considered the conclusive power so great that they had no doubts when it came to recommendations.

Recommendation #1

More than a dozen randomized trials of the effects of fat-controlled diets or drugs permit the conclusion that reduction of blood cholesterol levels in people with relatively high initial levels will reduce the rate of coronary heart disease. This has been shown most convincingly in men with a high cholesterol level, but although direct intervention studies have not been conducted in women, there is no reason to propose a separate treatment schedule for women.

Nothing was said about the fact that most trials did *not* demonstrate any benefit (in fact both the number of deaths and the number of heart attacks had *increased* in some of them); or that in most studies high cholesterol has not been associated with an increased coronary mortality for women.

Recommendation #2

Individuals in the high-risk group (above 6.2 mmol/l (242 mg/dl) at an age of 30-39; above 6.7 mmol/l (261 mg/dl) at an age above 40) should primarily have intensive dietary treatment requiring a major effort on the part of physicians, nutritionists, dieticians, and other health professionals. If this treatment does not work, drug therapy should be used.

Thus, only in the United States, tens of millions of healthy individuals should be on a diet. Let's hope that there are enough health professionals to carry out this daring project.

The drug producers and their stock holders should be happy, because, as you now know, it is extremely difficult to lower blood cholesterol with diet alone. The panel also knew it: after all, the control individuals in the LRC trial had eaten the recommended diet, and their cholesterol decreased less than one percent. No doubt about it—drugs would be necessary.

Recommendation #3

Individuals with moderate-risk blood cholesterol (above 5.7 mmol/l (220 mg/dl) at an age of 30-39; above 6.2 mmol/l (240 mg/dl) at an age above 40), — the upper 25 percent on the cholesterol scale — should also have intensive dietary treatment, and if other risk factors were present, drug therapy should be considered.

Further tens of millions of Americans on drab diet and dangerous drugs! In the LRC trial those from the upper 0.8 percent on the cholesterol scale were treated, and with drugs. And only after enormous effort could the trial directors come up with a result that nobody but a statistical incompetent could see as positive.

If it is that difficult with drugs to improve the prognosis for people with the most extreme cholesterol levels, how can diet alone produce a benefit for those with no more than a moderately high cholesterol?

Recommendation #4

Blood cholesterol is too high in most Americans because they eat too much saturated fat, too many calories, and too much cholesterol.

To avoid conflicts between the proponents, the recommendations included *all* the suggested diets.

Recommendation #5

Therefore, all Americans except children below the age of two are recommended a diet with no more than 250-300 mg cholesterol per day, and a reduction of total saturated fat intake to 10% or less of total calories, and an increase of polyunsaturated fat intake but to no more than 10% of total calories. The goal is to reduce blood cholesterol in the entire population to less than 5.0 mmol/l (195 mg/dl).

Here everybody is urged to eat what was originally advised for the high-risk group, except that people with normal cholesterol do not get help from health professionals. These people, the majority, have to judge for themselves when the magical ten per cent limit for polyunsaturated fat has been reached, the limit between harmless and dangerous amount. Nobody knows how the panel members found just that limit as crucial; nor why they chose a cholesterol limit of 195 mg/dl (5 mmol/l). (Every authority sees to have his own limit; the chosen value was probably determined by a vote).

Recommendation #6

There is no direct evidence of the benefit to be expected in the elderly, but dietary treatment may still be helpful.

Apart from the fact that there is no evidence either for the rest of mankind, why should we sour the lives of the elderly with an unpleasant diet if its benefit has never been proven? And remember you belong to the elderly as soon as you reach the age of forty-seven.

Recommendation #7

Also children should have treatment but not before the age of two. If blood cholesterol is above 4.4 mmol/l (172 mg/dl) diet is recommended; if it is above 5.2 mmol/l (203 mg/dl), drugs should be given, for instance, cholestyramine.

Poor kids! Remember that two out of three trial subjects given cholestyramine had gas, heartburn, belching, bloating, abdominal pain, nausea, vomiting, constipation or diarrhea.

Recommendation #8

If the American population follow the recommendations of the National Cholesterol Education Program, substantial improvements are in sight. For instance, if the cholesterol is lowered by

five percent, the risk of having a heart attack will be reduced by ten percent.

These figures, which are cited in all official papers on cholesterol and diet, are grossly misleading. The risk of having a heart attack in the LRC trial was lowered from 9.8 to 8.1 percent, a difference of only 1.7 percentage point. This equals 0.2 percentage point for each percent of cholesterol lowering, which means a total of only one percentage point if blood cholesterol is lowered by 5 percent. But this whole line of reasoning is absurd because, after all, the LRC trial did not lower the number of heart attacks more than could be explained by chance.

Recommendation #9

The absolute magnitude of this benefit should be greater in patients at high risk from existing coronary heart disease or the presence of other risk factors such as cigarette smoking and hypertension.

This statement is preposterous. The calculations mentioned above were based on the figures from the LRC trial which studied no one but high risk individuals.

No reservations

The panel had no reservations except to say that a number of problems should be investigated in the future (thus ensuring huge amounts of future government welfare for scientists and research doctors). They suggested for instance, that more information should be gained about the possible danger of eating great amounts of polyunsaturated fat. Let us hope that a diet, very high in polyunsaturated fatty acids is not harmful, but it would have been wise to perform such studies before launching a campaign to reform everyone's diet.

The document prompted protests from many scientists, but, as we know, without any impact whatsoever. The cholesterol campaign has flourished ever since then and has spread to many other countries. Rumors are circulating that Ancel Keys has been suggested as a candidate for the Nobel prize.

Nothing was mentioned in the consensus report about the numerous unsupportive studies I have discussed in this book. And contrary to the initial statement of the consensus report many scientists have not agreed about the dangers of fat food and cholesterol. In the next chapter I shall present some of the critics and their objections.

Insider Insight

From a George Lyman Duff memorial lecture:

“A final lesson worth noting is that the current cholesterol campaign represents a rare concordance of interests on the part of many constituencies. The health professions, the pharmaceutical industry, government, the public—all should benefit from efforts to promote and implement the recommendations and guidelines in the Adult Treatment Panel report. Physicians will benefit because they will be providing better medical care to their patients and incidentally will have available a new and expanded market of patients for preventive medical care. The pharmaceutical industry will benefit from the greatly expanded market for cholesterol-lowering drugs that will result from even the most careful application of the guidelines on a national scale. The public will benefit from reductions in coronary risk and disease. And government will benefit from better health of its citizens and from reduced national expenditures that should result from reductions in coronary risk and disease.

“Moreover, this concordance of interests should promote cooperation—even collaboration—on the part of these various constituencies, something that is indeed occurring in part in quite a gratifying way.

“In closing, I’d like to acknowledge the pleasure I’ve had in playing an active role in the national cholesterol campaign. It has been a most exciting year—and a great pleasure this evening to be able to share some of my thoughts with friends and colleagues in the cholesterol and cardiovascular communities.”

Myth 10: All Scientists Support the Diet-Heart Idea

Only dead fishes go downstream.

Polish proverb

At this point you may probably wonder why you haven't heard about all this controversy before and why not even your doctor knows anything.

Criticism has been raised—a great deal of criticism. But it has been presented in journals and books that are not easily accessible to the layman, and critical voices have been drowned out in a flood of papers from the proponents. And the media, supported in large part by advertising revenues from pharmaceuticals and a food industry that has found it extremely profitable to use vegetable oils instead of animal fats, has consistently ignored the voices of dissent while hyping the recommendations for expensive drugs and dietary change.

Furthermore, as I have exemplified here and there in the previous chapters, the pontiffs of the cholesterol crusade systematically ignore the contradictory findings. And the same people are brilliant in finding the few studies that apparently are in support, and if they are not, a magic spell may change the picture. And don't forget that if your research is in accord with the wizards view, financial support from the drug and the food industry is almost endless. If not, you may risk both your funding and your position. Let me just remind you about Kilmer McCully, the American researcher who discovered the association between homocysteine and atherosclerosis. When he published his observation that the homocysteine, not the cholesterol concentration in the blood was associated with degree of atherosclerosis, he lost his position at Harvard Medical School and Massachusetts General Hospital and for two years he wasn't able to get a new one anywhere.[\[268\]](#)

And there are more brave researchers. Presented here, in alphabetic order, are a few of those who have had the courage to swim against the current. All of them have produced a large number of scientific studies of which I shall mention only the most important.

Mary Enig[\[269\]](#)

is an international expert in the field of lipid biochemistry, a nutritionist and a consulting editor to a number of scientific publications, including the Journal of the American College of Nutrition. She is also President of the Maryland Nutritionists Association. Her main research has concerned the hazards associated with consumption of trans fatty acids. She has published many scientific papers on the subject of food, nutrition, and food fats and oils; several chapters on nutrition for text books; and a primer for laymen and professionals on fats, oils and cholesterol. When asked whether saturated fats cause heart disease, she replied:

“The idea that saturated fats cause heart disease is completely wrong, but the statement has been ‘published’ so many times over the last three or more decades that it is very difficult to convince people otherwise unless they are willing to take the time to read and learn what all the economic and political factors were that produced the anti-saturated-fat agenda.”

Michael Gurr[\[270\]](#)

was previously an associate professor of biochemistry at the School of Biological & Molecular Sciences in Oxford, previously editor-in-chief of *Nutrition Research Reviews* and editor of three other scientific journals. In a recent 50-page review published in *Progress in Lipid Research*, he presented the arguments of the cholesterol hypothesis in a thorough and honest way along with all the weaknesses of the theory. His main objections were the insufficient correspondence in vascular pathology between animal models and man and between familial hypercholesterolemia and atherosclerosis; the flaws and selection bias in the epidemiological evidence; the lack of correspondence between trends in coronary mortality and fat consumption patterns; the weak prediction achieved by measuring blood cholesterol; and the lack of improvement in mortality after dietary and pharmacological lowering of blood cholesterol. Professor Gurr’s final words provide a fitting summary of everything that we have discussed in this book:

“The arguments and discussion of the scientific evidence presented in this review will not convince those ‘experts’ who have already made up their

minds, for whatever reason, be it truly scientific or political, that a fatty diet is the cause of CHD. However, I hope that some readers, who were, perhaps, unaware that the lipid hypothesis had any shortcomings, will have been persuaded that the relationships between the fats we eat and the likelihood that we may die from a heart attack is by no means as simple as these simplistic statements imply.”

George Mann[271]

was previously a professor in medicine and biochemistry at Vanderbilt University in Tennessee. From his studies of the Masai, he realized that animal fat could not possibly be the main cause of high cholesterol and coronary heart disease. As long ago as 1977, in the *New England Journal of Medicine*, he presented his main arguments against the diet-heart idea:

“the lack of relationship between dietary habits and blood cholesterol, the lack of correlation between this century’s trends in fat consumption and death rates in the United States, and the disappointing outcome of the cholesterol-lowering trials.”

Eight years later, when the cholesterol education campaign was getting into gear, Professor Mann summarized his criticism of the diet-heart idea in *Nutrition Today*. *“The diet-heart idea is the greatest scientific deception of our times, perhaps of any time,”* he said. Mann is especially critical of the cholesterol-lowering trials. *“Never in the history of science have so many costly experiments failed so consistently, he declared.”*

Professor Mann severely criticized the LRC directors. The unsupportive results from the LRC study have not prevented them from *bragging about this cataclysmic breakthrough*. And he continued:

“The managers at the National Institutes of Health have used Madison Avenue hype to sell this failed trial in the way the media people sell an underarm deodorant. The Bethesda Consensus Panel... has failed to acknowledge that the LRC trial, like so many before it, is saying firmly and loudly:

‘No, the diet you used is not an effective way to manage cholesterolemia or prevent coronary heart disease and the drug you so generously tested for a pharmaceutical house does not work either.’”

People who are faced with the many distorted facts about diet, cholesterol and heart disease often ask me why almost all scientists unquestioningly accept the diet-heart idea. And you may have asked the same question after reading this book. Here is Professor Mann's comment:

"Fearing to loose their soft money funding, the academicians who should speak up and stop this wasteful antiscience are strangely quiet. Their silence has delayed a solution for coronary heart disease by a generation."

Professor Mann offers a little glimpse of hope at the end of his article in *Nutrition Today*:

"Those who manipulate data do not appreciate that understanding the nature of things cannot be permanently distorted—the true explanations cannot be permanently ignored. Inexorably, truth is revealed and deception is exposed... In due time truth will come out. This is the relieving grace in this sorry sequence."

Edward Pinckney

was previously an editor of four medical journals and former co-editor of the *Journal of the American Medical Association*. In 1973, he published a book called *The Cholesterol Controversy*, which summarized all the inconsistencies in the cholesterol idea.[\[272\]](#) It seems impossible that any sensible and honest doctor who has read this book could continue to teach his patients about the dangers of cholesterol.

Pinckney describes all the factors that influence blood cholesterol in healthy people and how difficult it is to get a reliable measure of the cholesterol level due to uncertainties of the analysis:

"The level of one's blood cholesterol is, at best, nothing more than an extremely rough indication of a great many different disease conditions. At worst, it can be more the cause of stress and the diseases that stress brings on. To alter one's life-style as a consequence of this particular laboratory test may well cause more trouble than it could relieve."

Pinckney thoroughly describes the dangers of lowering one's cholesterol and devotes an entire chapter to the political drama preceding the cholesterol campaign. He had long wondered about the dairy industry's passive acceptance of the slurs against its products. The explanation he

found was that many dairy distributors also distributed polyunsaturated products at an even greater profit. And the dairy farmer does not protest because the federal government uses taxpayer money to buy the farmer's surplus butter at a price far higher than what he could make by competing on the open market.

The beginning of Chapter 1 in Pinckney's book is worth citing:

"Your fear of dying—if you happen to be one of the great many people who suffer from this morbid preoccupation—may well have made you a victim of the cholesterol controversy. For, if you have come to believe that you can ward off death from heart disease by altering the amount of cholesterol in your blood, whether by diet or by drugs, you are following a regime that still has no basis in fact. Rather, you as a consumer have been taken in by certain commercial interests and health groups who are more interested in your money than your life."

Raymond Reiser[\[273\]](#)

was a professor of biochemistry at Texas A & M University. In 1973 he criticized the recommendations for dietary treatment of high cholesterol by declaring:

"The authority quoted by these authors for the recommendation is not a primary source but another review similar to their own. It is this practice of referring to secondary or tertiary sources, each taking the last on faith, which has led to the matter-of-fact acceptance of a phenomenon that may not exist."

In his paper, Reiser continued with a thorough 30-page review of almost all experiments on the influence of dietary fatty acids on blood cholesterol levels. His main conclusions were that most experiments are biased by serious faults, that limited time frames and too few test individuals have been used, and that the diet studied has been too extreme to allow conclusions that are valid for ordinary people...

"One must be bold indeed to attempt to persuade large segments of the populations of the world to change their accustomed diets and to threaten important branches of agriculture and agribusiness with the results of such

uncontrolled, primitive, trial-and-error type explorations. Certainly modern science is capable of better research when so much is at stake.”

More recently, Reiser analyzed the references used as support by the American Heart Association in its rationale for its dietary recommendations. He could not find any supportive studies. In fact, some of the studies had results that contradicted the diet-heart idea:

“Thus the rationale is not a logical explanation of the dietary recommendations but an assemblage of obsolete and misquoted references. Since rational explanations for the recommendations are essential for their acceptance, the public to whom they are addressed is justified in remaining skeptical of them.”

Paul Rosch[274]

is President of the American Institute of Stress, Clinical Professor of Medicine and Psychiatry at New York Medical College, Honorary Vice President of the International Stress Management Association and Chairman of its US branch. He is the editor or subeditor of three well-known medical journals, and he has served on the board of several other journals. He has served as President of the New York State Society of Internal Medicine, as Chairman of the International Foundation for Biopsychosocial Development and Human Health and has been an Expert Consultant on Stress to the United States Centers for Disease Control. He has written extensively over the past forty-five years on the role of stress in health and illness, with particular reference to cardiovascular disease and cancer. He has appeared on numerous national and international television programs such as *The Today Show*, *Good Morning America*, *60 Minutes*, *Nova* and on *CBS*, *NBC*, *PBS*, *BBC* and *CBC* network presentations. His editorials and comments have been published in every major medical journal, and he has also been interviewed and widely quoted in numerous major American newspapers and magazines.

As the author of the *Newsletter of the American Institute of Stress*, Professor Rosch has published several articles about the cholesterol hypothesis and the diet-heart idea. His conclusions are close to those presented in this book:

“A massive crusade has been conceived to ‘lower your cholesterol count’ by rigidly restricting dietary fat, coupled with aggressive drug treatment. Much of the impetus for this comes from speculation, rather than any solid scientific proof.”

“The result is well-known. The public is so brainwashed, that many people believe that the lower your cholesterol, the healthier you will be or the longer you will live. Nothing could be further from the truth.”

How can this go on year after year? Professor Rosch has several explanations:

“The cholesterol cartel of drug companies, manufacturers of low-fat foods, blood-testing devices and others with huge vested financial interests have waged a highly successful promotional campaign. Their power is so great that they have infiltrated medical and governmental regulatory agencies that would normally protect us from such unsubstantiated dogma.”

Rosch reminds us that practicing physicians get most of their information from the drug companies. But... *“compared to their peers a half century ago, most doctors don’t have the time or skills to critically evaluate reports, very few know anything about research, nor did the generation that taught them.”*

Now in his eighties, Rosch is still active and his critical voice appears now and then in the scientific press.

Ray Rosenman[\[275\]](#)

is the retired Director of Cardiovascular Research in the Health Sciences Program at SRI International in Menlo Park, California, and previously associate Chief of Medicine, Mt. Zion Hospital and Medical Center in San Francisco. He has been a cardiologist and a researcher since 1950. He has published four books, many textbook chapters and numerous journal articles about cardiovascular diseases. His main interest has been the influence of neurogenic and psychological factors on the blood lipids, but he has also written reviews critical of the diet-heart idea. Here is the conclusion from his most recent review:

“These data lead to a conclusion that neither diet, serum lipids, nor their changes can explain wide national and regional differences of CHD

[coronary heart disease] rates, nor the variable 20th century rises and declines of CHD mortality.”

“This conclusion is supported by the results of many clinical trials which fail to provide adequate evidence that lowering serum cholesterol, particularly by dietary changes, is associated with a significant reduction of CHD mortality or improved longevity. It is variously stated that the preventive effects of dietary and drug treatments have been exaggerated by a tendency in trial reports, reviews, and other papers to cite and inflate supportive results, while suppressing discordant data, and many such examples are cited.”

Russell Smith[\[276\]](#)

was an American experimental psychologist with a strong background in physiology, mathematics and engineering. In cooperation with Edward Pinckney, he studied all aspects of the diet-cholesterol-heart issue with extreme thoroughness and presented his findings in two large scientific reviews of the literature containing more than 700 pages with more than 3000 references, as well as in a popular book. No review written by the proponents of the diet-heart idea can compare with Russell Smith's books when it comes to completeness and scientific depth. Volume 1 of his review is an overview of the entire issue. Smith's summation is devastating for the diet-heart proponents:

“Although the public generally perceives medical research as the highest order of precision, much of the epidemiologic research is, in fact, rather imprecise and understandably so because it has been conducted principally by individuals with no formal education and little on-the-job training in the scientific method. Consequently, studies are often poorly designed and data are often inappropriately analyzed and interpreted. Moreover, biases are so commonplace, they appear to be the rule, rather than the exception. It is virtually impossible not to recognize that many researchers routinely manipulate and/or interpret their data to fit preconceived hypotheses, rather than manipulate hypotheses to fit their data. Much of the literature, therefore, is nothing less than an affront to the discipline of science.”

Russell Smith concluded:

“The current campaign to convince every American to change his or her diet and, in many cases, to initiate drug “therapy” for life is based on fabrications, erroneous interpretations and/or gross exaggerations of findings and, very importantly, the ignoring of massive amounts of unsupportive data... It does not seem possible that objective scientists without vested interests could ever interpret the literature as supportive.”

In his books and papers Russell Smith criticized a large number of leading scientists from the National Heart, Lung and Blood Institute and the American Heart Association, which he calls the alliance. He considered their work incompetent and sloppy:

“The fraud is so blatant and so pervasive that it was considered necessary to take some liberties with the usual staid rhetoric of a scientific review and inject stronger language to emphasize the problem.”

Russell Smith was aware that he was up against some extremely powerful institutions:

“The political and financial power of the NHLBI and AHA team... is enormous and without equal. And because the alliance has substantial credibility in the eyes of the public and most practicing physicians, it has become a juggernaut, able to use its power and prestige to suppress a great body of unsupportive evidence and even defy the most fundamental tool of scientists, logic.”

The scientists who have produced the misleading papers and reviews are, of course, the first with whom Russell Smith finds fault. But he added:

“Equally culpable are the editors of the many journals who publish articles without regard to their quality or scientific import. It is depressing to know that billions of dollars and a highly sophisticated medical research system are being wasted chasing windmills.”

William Stehbens[\[277\]](#)

a former professor at the Department of Pathology, Wellington School of Medicine, and director of the Malaghan Institute of Medical Research in Wellington, New Zealand, is another articulate critic. Based on his own studies and on extensive reviews of the literature, he has effectively

demonstrated the many fallacies of the diet-heart idea. In a thorough review of the experimental studies he concluded:

“Upon examination of this evidence and consideration of the specific criteria for the experimental production of atherosclerosis, any pathologist of independent mind and free from preconceived ideas would conclude that human atherosclerosis and the lesions induced by the dietary overload of cholesterol and fats are not one and the same disease.”

Stehbens has also pointed out the weaknesses of the epidemiological studies that have used mortality statistics as proof for causality:

Continued, unquestioned use of unreliable data has led to premature conclusions and the sacrifice of truth. The degree of inaccuracy of vital statistics for CHD is of such uncertain magnitude that, when superimposed on other deficiencies already indicated, the concept of an epidemic rise and decline of CHD in many countries must be regarded as unproven, and governmental or health policies based on unreliable data become completely untenable.

According to Stehbens, atherosclerosis is due to wear and tear of the arteries, and not to high cholesterol levels in the blood, an idea he supports with many good arguments.

The following words from a 1988 paper summarize Stehbens’s view on the diet-heart idea:

The perpetuation of the cholesterol myth and the alleged preventive measures are doing the dairy and meat industries of this and other countries much harm quite apart from their potential to endanger optimum nutrition levels and the health of the populace at large.... It is essential to adhere to hard scientific facts and logic. Scientific evidence for the role of dietary fat and hypercholesterolemia in the causation of atherosclerosis is seriously lacking... The lipid hypothesis has enjoyed undeserved longevity and respectability. Readers should be aware of the unscientific nature of claims used to support it and see it as little more than a pernicious bum steer.

Lars Werkö[\[278\]](#)

was previously a professor of medicine at Sahlgren’s Hospital, Gothenburg, Sweden, scientific director at the Astra Company, and then head of the

Swedish Council on Technology Assessment in Health Care, a governmental agency. Professor Werkö has been an opponent of the diet-heart idea for many years. In 1976 he criticized the design of the large epidemiological studies aimed at preventing coronary heart disease, most of all the Framingham study.

According to Werkö, the dogma is based on questionable “facts” rooted in hopes, wishful thinking and studies using selected materials.

“No studies have proved anything, but instead of formulating new hypotheses, diet-heart supporters call the current one the most probable truth, and they have intervened in people’s lives because they will not wait for the final proof.”

In another paper, he pointed to a number of inaccuracies and sloppy data gathering in the MR.FIT trial.

At the age of 90 Werkö is still active. Recently he was awarded by the Swedish medical journal *Dagens Medicin* for his many critical contributions to today’s debate around Swedish health care.

Epilogue

After a lecture, a journalist asked me how she could be certain that my information was not just as biased as that of the cholesterol campaign. At first I did not know what to say. Afterwards I found the answer.

She could not be certain. Everyone must gain the truth in an active way. If you want to know something you must look at all the premises yourself, listen to all the arguments yourself, and then decide for yourself what seems to be the most likely answer. You may be easily led astray if you ask the authorities to do this work for you.

This is also the answer to those who wonder why even honest scientists are misled. And it is also the answer to those who after reading this book, ask the same question.

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Patel C. The lipid research clinic's trial. The Lancet 1, 633-634, 1984. Patel has calculated that if the result of the LRC trial is transferred to England and Wales one of every 400 coronary deaths could be saved each year, amounting to the cost of about £140 million a year and of gastrointestinal side effects in more than 130 000 healthy individuals.

Editorial. The Lancet 1, 333-334, 1988. The author stressed the fact that there is little correlation between dietary fat intake and cholesterol level; that no convincing dietary prevention study had been published; and that the increase in deaths from other causes in the drug trials “cannot be ignored simply because it did not form part of the hypothesis that these trials were designed to test.”

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MY DOCTOR TOLD ME

Medical Myths That
Can Harm Your Health

Ken D. Berry, MD, FAAFP



**UPDATED &
EXPANDED
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Morgan, and Abby Grace; and
my granddaughter, Adeline Virginia.
You all are my saving grace
and my inspiration.**

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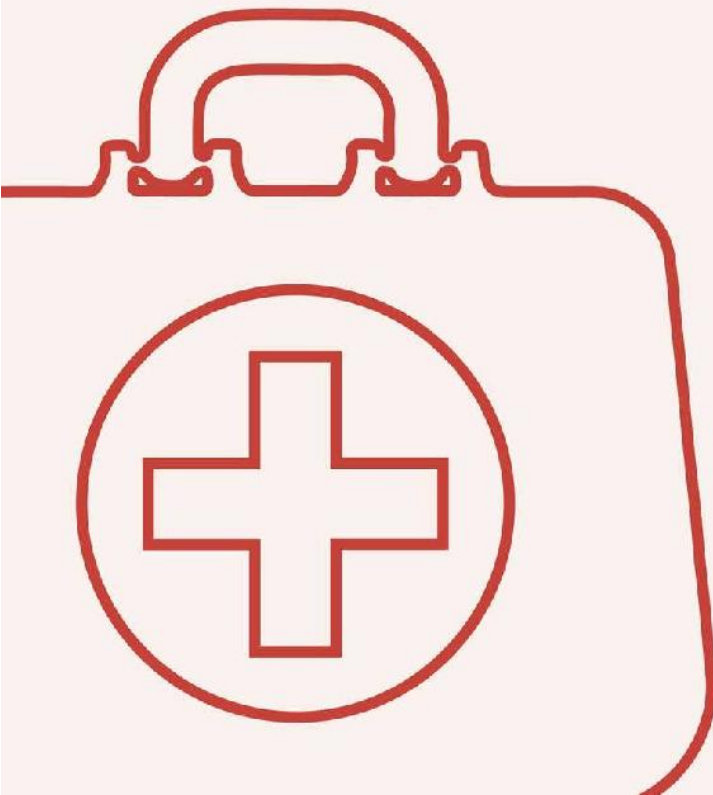
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FOREWORD



The first time I picked up *Lies My Doctor Told Me*, I immediately recognized someone who had the same fire in his belly as I do. Dr Ken Berry has put down in simple language the tragic idiosyncrasies of medicine that are doing patients harm. That the medical profession continues to perpetuate the spread of certain information is ample justification for the confronting title of *Lies My Doctor Told Me*. It immediately makes you pay attention, and I am fine for that.

Lies My Doctor Told Me is a survival kit for both patients and doctors alike.

This is not a book about “doctor bashing” as much as a resource for all parties to create an open discussion regarding healthy options. Patients want and need to be better informed, and doctors need to be able to discuss openly the information that’s widely available to patients. The adage of “Trust me; I am a doctor,” no longer has the credibility of yesteryear.

Doctors are becoming far more accountable to their patients, and the only way for doctors to “survive” is to read more, in and around medicine. You may be a doctor and be in complete agreement on what you read in this book. You may, on the other hand, find this text disconcerting, but I can assure you that too many doctors across the globe practice the myths covered in *Lies My Doctor Told Me*. My travels and communications assure me of that.

Patients need to be informed of the misconceptions that lurk out there—particularly in the doctor’s office.

The intent of this book is not necessarily to blame individual doctors; rather the purpose is to consider the health-washing of their medical education that has been tainted by vested interests—including the pharmaceutical and food industries—and ideological bias. The more you look, the more you find the agendas of industry and ideology that have affected research outcomes. There is no greater manipulation than in the field of “nutrition science,” and *Lies My Doctor Told Me* spends some time denouncing myths in that arena.

We as a profession are largely to blame. We became confused in believing that “nutrition science” was the same as “medical science.” The former has been promoted by the food industry for 100 years and is based around improving profit, palatability, shelf-life, transportability, and, lastly, health. Medical science should be based on the scientific method that incorporates observation, hypothesis, testing, conclusion, and cautious implementation with ongoing review. This remarkable oversight that resulted in linking the two and calling “nutrition science” a “science” may be the biggest human health tragedy of all time.



My journey into the myths of medicine has been like that of Ken's. I had numerous health issues of my own despite following conventional, traditional, and "mythical" guidelines, and I paid the price for that. It was when I started challenging those entrenched dogmas, particularly around nutrition, that I found that virtually everything was a house of cards, collapsing with the simplest of questions of the so-called research and nutrition science.

I am fairly certain that Ken asked me to write this foreword to the updated version of *Lies My Doctor Told Me* for being a fellow doctor who dared to challenge peer-reviewed nutritional guidelines and was "reprimanded" accordingly, with the threat of medical deregistration. I raised the issue of the quality of hospital food and its effect on patient safety, and I was punished accordingly. I was effectively "silenced" from recommending for my patients a diet based on fresh, local, and seasonal produce—essentially meat and vegetables without added sugar, loads of carbohydrates, and nutrient-deficient processed food.

Vested interests working against me included a medical system stuck in its own timeless dogma, a cereal food industry that identified me as a problem, and a medical registration and censorship system that could not bring itself to admit its failings.

With the support of many people in our local and international community, combined with the double-edged sword of social media, common sense finally prevailed. After nearly five years, the determination against me was overturned with a formal apology.



Through social media platforms, Ken and I have become friends, although we've never met directly. We are kindred spirits, and it has been a joy to link with him and other forward-thinking health professionals across our planet. The Internet has closed distances for us all; when we do meet up, there will be plenty of time made to chew the fat.

Lies My Doctor Told Me is something I would have loved to write. I agree with the entire concept. This second edition adds chapters that enhance the wealth of information of the first edition.

Calling out the lies and the perpetrators in any situation is an uncomfortable experience for all, but it's the only way forward in seeking reform. The health, and ultimately the wealth, of modern society is on the line. The future for our children hangs in the balance. I used to be concerned primarily by environmental effects for the future, but that "future" is distant. Our health is in the balance today.

Unfortunately, we are confronted by a health system that does not encourage the lengthy medical consultations that we need for true health education for patients. The business model that accompanies health provision that exists in many countries is just not designed for that "luxury." It suffers from a "medicate or operate" model that has been around for 100 years.

"Half of what you are taught as medical students will in ten years have been shown to be wrong. And the trouble is, none of your teachers know which half." Dr. Sydney Burwell announced this now famous quote at a dinner while he was Dean of Harvard Medical School in the late 1930s. It was provocative then but has endured to this day.

In my thirty-five years as a medical practitioner, at least half of what I can remember from medical school is now defunct. If we continue to accept this concept of knowledge obsolescence, then at least half of our current guidelines are going to be proven incorrect, and therefore potentially harmful to the community.

My concern is that current opinion has become entrenched as guidelines that have become rulebooks for doctors. Dissenters do not get invited to be on guideline-recommendation committees. Challenging those guidelines, which often are influenced by vested pharmaceutical and food industry interests, has become a roadblock to progress.

Many doctors fear the wrath of their governing bodies for taking up the cause for quality assurance, the process of reviewing current practice given current information.

Medicine is at a crossroads, and this time it is about challenging paradigms. Our patients are challenging them for us via the learning fields of social media and the Internet, whether doctors like it or not.

Doctors must be accountable to our patients. You, as a doctor, may not agree with Ken's stand on the issues covered in *Lies My Doctor Told Me*, but you should be aware that the issues are all topical in 2019. Not being able to discuss them with your patients is going to cost you your patients' confidence. I hear from patients almost daily that they don't trust their doctors. That's a far cry from my early days as a consultant.

I am one of those doctors who took the path of resistance against entrenched paradigms, yet that direction was the right path for my patients. Ken reminds us that taking on the "guidelines" can be awkward, but he and I will continue to live and practice by this adage: Science evolves by being challenged. Not by being followed. You are welcome to join us.

Gary Fettke

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PREFACE



**The doctor is more to be
feared than the disease.**

—French proverb



This book will upset many doctors; it might even upset *your* doctor. If it does upset your doctor, that's a good sign that either you need to work on the relationship between you and your doctor, or you need to find a new one.

You see, there are two basic types of doctors. The most common type is comfortable where he is. He might read a little to keep up his CME (continuing medical education), but he has no real interest in reading deeply and broadly about medicine. This doctor readily accepts any new guidelines published by medical societies or the federal government. He doesn't care who paid for the research used to "prove" that a new pill works. He only wants to practice medicine with as little effort as possible. He considers himself the boss in the doctor-patient relationship. He believes he holds all the knowledge that matters, and the patient should listen respectfully and not question him.

If a patient suggests to this kind of doctor that they try something new or consider a new treatment, the doctor will become flustered, impatient, or angry. He doesn't seem to be interested in the uniqueness of each patient. This type of doctor believes he learned all he needed to know in his training and is not interested in continuing to learn. He will belittle, or berate, a patient who suggests that there may be another way to treat something. He is not happy at all if a patient brings information printed from the Internet to discuss with him. He will quickly let the patient know that he is the doctor and doesn't have time for such silliness. This kind of doctor will not like this book at all.



There is often so much politics in medicine that being right can actually get you into trouble.

The other type of doctor is an eager learner and a lifelong student. He reads deep in his own specialty, but he also reads about other specialties. He is always considering new treatments as well as ancient ones. This type of doctor is impressed when patients are concerned enough to learn about their symptoms and bring what they find to their office visits. He feels he is the patient's learned partner in health care rather than a dictator. This type of doctor is not offended when a patient speaks of chiropractic, naturopathy, or essential oils. When a patient shares printed information with him, covered in handwritten notes, he is excited because he knows this patient is very interested in their health. This type of doctor will most likely applaud this book.

THIS BOOK IS NOT MEDICAL ADVICE

This book is meant to stimulate thought in both doctors and patients. I want you as a patient to reexamine your health and any medical conditions you have. Are you doing the best you can to optimize your health? Is the advice you've received from doctors the best possible advice? I want you to read, research, and think about your health. Stimulating such action is what this book is for. This book is not medical advice. You should not start, stop, or change any medication based on what you read in this book. You should discuss those types of changes with your trusted doctor. If you don't trust your current doctor, then find a new one.



When writing about health and medicine, especially as a doctor, one has to be careful not to give medical advice. This medico-legal term, *medical advice*, refers to information you should receive only in a doctor-patient relationship, not from a book or website. Medical advice is something that can be given only by a provider to a patient in a particular scenario. This advice is given to the patient either in the hospital, clinic, urgent care, or, increasingly, during an online consultation. You should use the information in this book to become an expert on your health and medical conditions. You should use this book to form intelligent questions and requests for your doctor. You should not, however, change your medical regimen based solely on the contents of this book.

HOW TO USE THIS BOOK

You may not want to read this book from cover to cover, and there's no issue if you want to skip around or read only the chapters that apply to your health. Please underline, highlight, and write in this book. Fold down corners and copy and share this book all you want. I want it to help as many people as possible to experience their best health. The end of each chapter includes a homework section. If a chapter doesn't apply to you, then feel free to

ignore the homework. If, however, a chapter seems important to your unique health, then the homework section is where you can continue learning about the subject.

WHERE ARE THE WORKS CITED?

The ultimate purpose of this book is to encourage you to do your own thinking. I want you to think about your health and any diagnoses you've been given. To take charge of your health, you need to learn how to research health topics on your own. Because of this, and to keep the size of this book under control, I have omitted footnotes or lists of works cited. I'm not selling anything, so I have no motive to mislead you. I won't be pushing any supplements, powders, or pills on you; I just want you to be awake and aware of your health and the health care offered to you. You can use Bing.com, DuckDuckGo.com, or Google.com to search any health topic.

When you're ready to dive deeper into the medical research, you can go to PubMed.gov, type in your keywords, and search every medical research article in the world. This is the website doctors should use when looking for the latest research on a topic. With your Internet connection, a cup of coffee, and a few hours of research, you can be as knowledgeable as any doctor about your particular health issues. If you can answer your own medical question, then good; if you can't, then print out what you have researched, attach your notes, and take your research to a trusted doctor. He should be happy to discuss with you the information you've found.

PRONOUN USAGE

I debated how I would handle pronouns in this book. English is behind other languages in this area. We often must resort to the awkward *he or she* and *his or her* (as in "He or she should always respect his or her patient"). This is distracting to write and painful to read. Years ago, I had the idea of using *E*. Much as we use capital *I* to talk about ourselves, I thought there should be a way to say "he or she" more easily by using a gender-neutral capital *E*. It would save time and ink and be easier to read (for example, "E should always be respectful of patients"). I had full intention of using *E* in this book, but decided perhaps people were not ready for that yet. My wife, Neisha, suggested that I pick a pronoun and use it throughout the entire book. We discussed which pronoun I should use and decided a coin-flip

would be a fair way to decide. He/his won the toss, and so in this book I use he/his where pronouns are necessary. I will use she/her in the next book.

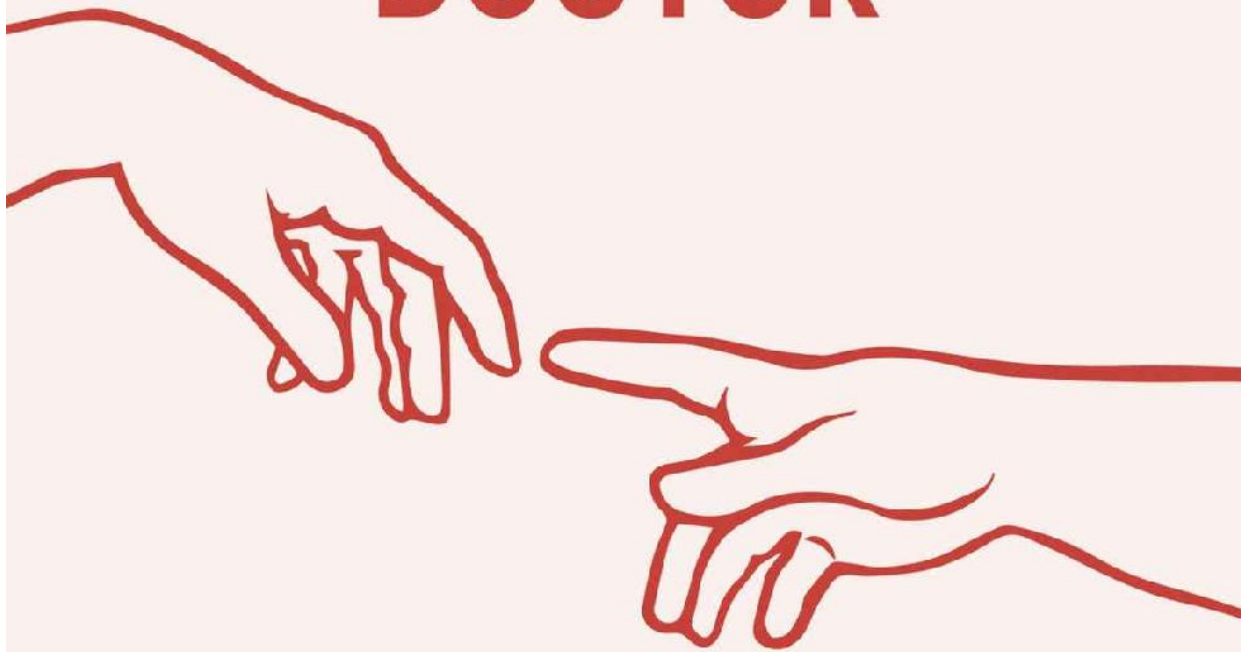
USE OF THE WORD *DOCTOR*

To make this book easier to read, I use the word *doctor* to refer to all health-care providers. The word *doctor*, as used in this book, can be used interchangeably with nurse practitioner, physician assistant, and nurse-midwife. Any of these health-care providers can tell you medical lies but also are capable of taking your health to the next level by telling you helpful medical truths. Regardless of which kind of provider you see, this book can help you improve your relationship with your health-care provider.



Chapter 1

TRUST IN GOD, NOT YOUR DOCTOR



**Though the doctors
treated him,
let his blood and gave him
medications to drink,
he nevertheless
recovered.**

—Leo Tolstoy, *War and Peace*



**Do you have a good working relationship with your doctor?
If not, you should keep reading. If you do, you still should
keep reading because what you are about to learn might
strengthen that relationship.**

I'm sure your doctor is a caring, kind, and thoughtful individual. However, he isn't superhuman, and he isn't God. Your doctor, at some point, had to possess intelligence and curiosity, or he would not be your doctor today. The path through college, medical school, residency, and medical practice is a very demanding, tricky road. As a result, not everyone can travel it. At some earlier point in his life, your doctor was an energetic, eager-to-learn, ready-to-try-new-things student who couldn't wait to learn everything possible and apply it to improving the health of his patients. What has happened to him since then? How did your doctor go from being an eager, curious learner, to a stuck-in-a-rut, bored, burned-out individual who just spent a whopping three minutes with you for your medical visit? That is a complicated question, and it varies from doctor to doctor.

In the following pages, I attempt to explain the thinking and motivation of your doctor to help you understand what's happening during the average office visit and give you a peek at what's going on behind the scenes and inside the head of your doctor. Let me begin by telling you the story of one doctor I know: me.

I went through medical school with 175 other individuals of all shapes, sizes, ethnicities, and genders. We had all done the work and suffered the hardships to get there for one reason: to become doctors. Some of my friends in medical school were there only because their families had demanded they go to either medical school or law school. Some were there only because they wanted to be the first person in the family to become a doctor. A few of my colleagues in medical school were just there for the money and the prestige. Honestly, those people were few and far between. Most of us had jumped through all the hoops required to get into medical school because we wanted to be important in our patient's lives, do great things, and help lots of people. We wanted to make the world a healthier place.



You can lead a doctor to knowledge, but you can't make him think.

I, like several of my classmates, was married and had a family as I went through medical school, which made the process much harder than it

would have been had I been single. I'm not saying a single person would not have had responsibilities aside from school, but single people would have been less likely to have responsibilities that would have felt slighted or betrayed if the promises made about life on the other side of medical school had not been kept. Medical school requires many hours of study, both solitary and in groups. My home away from home for the first two years was a small four-by-eight-foot room on the seventh floor of the library; it contained only a desk, a chair, and a lamp. I spent many of my waking hours as a young adult sitting and studying in that drab, depressing little study room.

As medical students, we would always vie for the best of these study rooms—the ones with a slightly bigger desk or a newer lamp. A fellow student and I once almost came to blows when I caught him stealing the comfy chair from my study room. It was a chair I had stolen fairly and squarely from another student's study room some months before. Those hours spent in my study room were hours I didn't get to spend with my family. I tried to make all those hours count so that when I became a doctor, I could somehow repay my family for the lost time. My children were growing up every day, and I was missing milestones of their development much more often than I would have liked. However, I had this calling and compulsion to become a doctor and be everything I imagined being a doctor must mean.

The problem with medical students (past and present) is that, unless one of their parents was a doctor, they don't really understand what it means to be a doctor. We had all watched the TV shows and read the books and dreamed the dreams. However, we had no idea what our daily lives would be like when we finished this journey. Looking back now, it seems a little crazy to have worked so hard and so long to attain a career about which we had little understanding of the daily workings.

The day-to-day life of a doctor was a mystery to us, but we still wanted to live it. Many doctors, when they finish this journey, are disheartened and disenchanted with the realities of their new careers. They regret their decision and the years they spent (wasted) making it their reality. However, there are school loans to pay and obligations to meet. The family waiting at home would be confused, dismayed, and disappointed if the new doctor in the family told them that despite the sacrifices they had endured, he wasn't at all happy with this new career. After all the work, sacrifice, and expense

to get through medical school, few doctors will walk away from their investment in this career, even if they discover they're miserable living the life of a doctor. You are therefore often left with a disheartened doctor who's doing something he doesn't love and who doesn't have any real interest in doing his best.

Regardless of the reasons why your doctor went to medical school, he is now a doctor—your doctor. You can be sure that his career, no matter how successful it appears to be, is not what he had hoped or dreamed it would be. His daily reality is nothing like the TV shows he watched, the books he read, or the dreams he dreamed. There is too much paperwork to read, millions of words of federal regulations to follow, employees to manage, bills to pay, and likely a family at home begging for more of his time. The weight of such things can stifle even the most brilliant and motivated mind. Instead of looking for the *best way*, a doctor often resorts to accepting the *least bad way* or is forced to comply with the *state-mandated way* of doing things. Primary care doctors are usually too busy to even think of doing any research or considering different or better ways of doing things. Being a doctor, business owner, and parent and doing each job well is more than most mere mortals can manage. Therefore, expecting a doctor to keep up with all the latest research so he can have independent thoughts about his patients' conditions is just too much to ask.

All these pressures and expectations can stifle a person's mind and extinguish any flicker of hope a doctor may have of doing new and great things in medicine. So, what is a poor patient (you) to do? Wake your doctor up. He doesn't voluntarily want to read, study, and think new thoughts. However, if you ask him respectfully, he will probably do it for you. If you word your request properly, you will develop a much stronger relationship with your doctor. You might also improve his partnerships with other patients. Being demanding, pushy, and loud is the opposite of what you should do.



I agree with what you're probably thinking: It shouldn't be your job to coddle and coax your doctor into going the extra mile for you and your health. However, even though your doctor's apathy toward learning new information is not your *fault*, it is your *problem*. You have only one life and one body to live it in, so you have to take ownership of helping your doctor to help you. If you take charge of the care of your body, you could avoid years of suffering and disease. I know, from being in the trenches of medical practice for more than a decade, what works and what doesn't when it comes to converting your doctor back into a curious, eager learner who is willing to work with you.

For years, I've had patients try every trick and strategy they could think of to get what they wanted from me, both good things and bad things. If what they wanted was a medication they didn't need, my answer was and still is, "This isn't Burger King; you can't have it your way." If what they wanted was for me to help them take their health and well-being to the next level, then I was more than willing to assist. I'm already receptive to alternative options and the ideas of optimization and true prevention, but most doctors are not. How can you tell whether your doctor is willing to learn? How can you find a doctor who is open to your ideas about your health?

The most powerful and most deceptive medical lie of all is that your doctor knows everything there is to know about your health or about medicine in general. A corollary to this lie is that medical scientists and researchers have discovered everything worth knowing about the human body and human health. As a doctor, I can tell you it would be nice to know everything. It's nice when patients place their trust in me and assume that I know everything. However, as a young doctor, I realized that not only were there many things I didn't know but there also were many things my mentors and professors didn't know. Doctors often carry themselves as if they know everything worth knowing. This is human nature. However, as a patient, you cannot let yourself be deluded into believing this. Your doctor is only as good as the knowledge he possesses and the effort he puts into staying current by looking for further knowledge and updates.

It's common for today's doctors to believe they have learned everything worth knowing. As a result, there seems to be little value in continuing the strenuous study they were used to in medical school. This way of thinking is the rule for most doctors in practice. Most of them will admit that they don't know details of new studies coming out, but they feel confident that the bedrock of their knowledge is solid and without cracks. State medical societies and boards aren't proactive about encouraging doctors to remain current in their studies. Also, the societies and boards do too much to prevent doctors from thinking outside the box or trailblazing new treatments or therapies.

Nothing will start a group of doctors grumbling quicker than mentioning that more continuing medical education should probably be required. The grumbling is about more than just not wanting to be told what to do. Many doctors have a real problem with cramming new knowledge into brains they already consider full. Even worse than a patient who believes their doctor knows everything is a doctor who believes this foolishness about himself. These issues are what you will be up against as you try to forge a meaningful partnership with your doctor or try to find one worth partnering with.

You can lead a doctor to knowledge, but you can't make him think. It's rare to find a doctor who stays energized and excited about the field of medicine and caring for patients. Most doctors quickly become comfortable in the rut of their medical practice. As a result, they learn only the bare minimum needed to stay current with their medical society's requirements,

and they do even that begrudgingly. Doctors are not bad or evil; they're simply human. To get the most out of this book, you need to realize several things. These things might seem simple-minded and obvious at first, but please think about each one. The main reason this book is necessary is that most patients and doctors have forgotten the following important facts.

You have only one life.

Your life is not a video game or a movie. Every decision you make about your health or allow your doctor to make for you, whether well-thought-out or foolish, can have an enormous effect on your long-term health and happiness. You don't get extra credit for blindly believing your doctor. You don't get a free pass just because your doctor told you to do something. If your doctor gives you bad advice, and you apply it to your health, it's you and your family who suffer, either a little or a lot, and perhaps for the rest of your life. Even if you can prove the doctor's error in court and successfully sue him for millions, you will still be the one left without some part of your health.



Your doctor is human.

Your doctor, despite his reputation or your belief in him, is only human, just like you. He is motivated by the same things that you are. He has the same weaknesses and makes the same sorts of mistakes. In spite of this truth, you should still hold your doctor to a higher standard. He should study and think harder than most other people you know. He should also strive to remain

current on a variety of medical subjects. However, you cannot blindly assume he does this; you must make sure. Only by establishing a partnership and building trust with a doctor will you be able to decipher whether he is an eager, lifelong student or doing the bare minimum to get by.



The doctor-patient relationship should be a partnership.

You should expect your doctor to have the latest and best medical knowledge. His job is to sift through tons of medical studies and textbooks and even to read far and wide outside the field of medicine. This research enables him to provide medical advice that is customized just for you—advice that honors your DNA and ensures that you have the best chance for a long, healthy life. You should expect your doctor not to give you incorrect or outdated advice. You should expect your doctor not to offer you a new pill just because of the slick ads and charming drug reps sent to him by Big Pharma. You should never blindly accept your doctor's advice, and you should trust your intuition about your health. You find true health by blending research, your health intuition, and your doctor's learned advice.



Research studies never tell the whole story.

Your doctor's job is to know this. However, because many doctors do such a poor job at extra study, and because your one life is at stake, you have to help. The Internet puts all the latest research within your reach. Therefore, to use this information to your best advantage, you should have a basic understanding of how medical research is conducted and, perhaps more importantly, who pays for it. Only so much medical research is conducted at any given time. This research costs billions of dollars to conduct, and someone must pay for it. Consequently, most medical research is paid for by Big Government or Big Pharma. Either choice has serious drawbacks. For scientists to conduct meaningful research, their thinking must be impartial and unbiased. Impartial and unbiased thinking is seldom used by Big Government and never used by Big Pharma.

No one can keep up with all the research.

So much medical research is published today that no doctor can possibly keep up with it all. A good doctor sifts through as much of this research as possible and decides which studies give useful conclusions that he can apply to the health of his patients. Conversely, he also must decide which studies are thinly veiled pseudoscience performed by Big Pharma to get their next billion-dollar baby (drug) approved by the FDA. A good doctor looks for and finds meaningful research within his specialty. A great doctor also searches for information from other specialties and other branches of science. This search for information he can use to prevent disease and to optimize your health should be his all-consuming calling.

This book is not an indictment of doctors.

Remember, I am a doctor. I don't intend to make doctors out to be the bad guys. My goal is to call attention to very correctable problems in the current thinking of most doctors and how they are educated. This book should serve as a wake-up call for both doctors and patients. Both groups need to step it up a notch.



Doctors, it is your job to remain as up-to-date as possible on current research and not to believe every word that comes out of Big Pharma-sponsored research or the charismatic drug rep's mouth.

Patients, this is your one life we're talking about. Nothing is more important to your long-term health than your diet and lifestyle. Stop being mentally and physically lazy. Stop blindly trusting your doctor and Big Pharma to give you a magic pill to fix the health problems your diet has caused. Stop expecting your doctor to have a magic treatment to correct the damage your lifestyle is doing. Think about your health, research the latest options, think about solutions, and ask your doctor thoughtful questions. If your doctor becomes upset by all your questions, then your partnership might not be working. It might be time to repair it or to look for a new partner. If you blindly take the advice of your doctor and he is wrong, you and your family will suffer. Doctors who give bad advice have a way, just like everyone else, of placing the blame elsewhere. Most doctors won't lose a minute of sleep if your health suffers because you followed their bad advice.

Your health is both robust and fragile at the same time. If your diet and lifestyle are correct, you almost can't get sick. If your diet and lifestyle are incorrect, you almost can't get well. You're the product of thousands of successful reproductions. Your DNA is the product of an awesome creation and the culmination of many generations of improving stock. All it takes is one wrong prescription or one unneeded medical test, and you could suffer a side effect that will devastate your health or end your life. You should never trust something so precious and valuable as your health to the opinion of one person—not even your doctor.



Chapter 2

SO WHAT'S GOING ON HERE?



**The life so short, the craft
so long to learn.**

—Hippocrates



Who am I, anyway? I am a board-certified medical doctor, recently accepted as a fellow in the American Academy of Family Medicine, which is kind of a big deal for a family doctor. I've been practicing medicine in a small Southern town for more than a decade and have slowly become more and more aware of the failings of modern medicine. If you break your leg or rupture your appendix, modern medicine is what you need. If you are relatively healthy and are interested in both optimizing your health and working toward true, meaningful prevention of disease, then modern medicine will probably let you down.

I am planted firmly in the middle of both the good and the bad that is modern medicine. I never wanted to be part of the problem, but looking back now, it's obvious I was. The small, rural county in which I have practiced my entire career was recently named one of the unhealthiest counties in Tennessee, which made me feel like a failure. I was getting paid well to set a terrible example and give terrible advice to my patients. When I started my practice, I was young and thin, and I was in superb health. As the years went by, my diet kept getting worse, and I was always too busy to be more active.

A few years into my career, I had my lab values checked and was shocked to find that I was becoming diabetic. That was not something I was okay with at all. One day, I got short of breath trying to tie my shoes. I've always tried to give good advice and set a good example, but it became apparent that I was doing neither. I realized it was both comical and embarrassing that I was telling patients every day that they needed to lose weight while my belly made it look like I might go into labor at any moment.

My “waking up” has been a years-long process, starting with the self-discovery that I was an obese doctor who expected my patients to take my advice about weight loss and health. I started applying my natural inclination and ability to question everything and accept nothing blindly to the study of medicine for the first time. The deeper I researched, the more I realized just how ignorant I was. I've always had the natural ability (some would call it a curse) to question what the experts in any field say. Sometimes this ability gets me into trouble. However, this time it cleared the way for me to become a better doctor. Since our bodies are made of the food we've eaten, I thought nutrition would be a great place to start. I dug through the boxes containing all my notes from medical school, pulled out everything I had been taught about nutrition, and looked it over.



Patients should be able to trust their doctors to be intellectually honest. They aren't paying for good-sounding random answers to their medical questions.

Because nutrition is so important to good health, I'm sure you are imagining a huge stack of books and notes on my desk, right? Instead, I

found only one half semester's worth of notes and a small paperback book. I could hold it all comfortably in one hand. No joke—that's the total of what the 175 of us learned about nutrition in four years of medical school. A biochemistry professor who was a native of New Zealand had given most of our nutrition lectures. All I could remember was his accent and the interesting way he said pasta (*paasssta*). I remember how he said the word both because of the way he said it and because of the number of times he said it.

During his few lectures, he shared with us that he was a brittle diabetic. He also told us about the many servings of whole-wheat pasta he ate daily, trying to keep his blood sugar under control. As a medical student, I did not understand how the two were related or how ridiculous his statement was. The lesson we medical students learned was that somehow lots of servings of whole-wheat pasta must be good for diabetics. Looking in the mirror at my fat belly, I realized that eating lots of whole-wheat pasta wasn't working for my patients or me. Increasingly convinced that I was ignorant of the nutrition needed to nourish the human body, I studied nutrition for the first time in my medical career.

First, I assumed that studying nutrition textbooks and journals would be the proper approach. I quickly realized that big food corporations sponsor publication of most of this information, and the publications offer little that would help in prevention and healing. Next, I looked at the Atkins Diet. In medical school, we learned that this diet could be bad for your kidneys, and we were told we probably shouldn't recommend it to patients. When I looked at the research the first time, the conclusions of most of the studies seemed to support this belief. When I looked again, this time at the whole of the research and not just the conclusions of the studies, I realized that the findings didn't support the conclusions. It was a weird awakening for me as a doctor. It's common practice for a busy doctor to read only the conclusion of a research paper, not the entire paper. Doctors do this because of their justifiable assumption that the conclusion should honestly sum up the research, findings, and take-home message of the research in a few hundred words.

It turns out that the researchers often slant the conclusions of studies toward what the researcher thinks or wants the study to show or not show. Even worse, conclusions are often tainted by the desires of the Big Pharma or Big Food corporation that sponsored the study. I decided the Atkins Diet

wasn't as dangerous as I'd been led to believe. Therefore, I tried it myself. I lost 20 pounds in two months, and my kidney function was better than it had been before I started! My problem with the Atkins Diet was that I actually like veggies and berries and missed eating them. I got bored eating rib-eye steak and butter all the time (true story). I looked at the South Beach Diet, the Ornish Diet, and a few others. Then I found a book called *The Primal Blueprint* by Mark Sisson. It spoke to me and changed my paradigm about nutrition, health, and medicine. This diet tried to mimic a primal or Paleo diet, like the one our ancestors ate thousands of years ago.

Here's the thinking that sold me on primal/Paleo as the best possible way for humans to eat and live. Human DNA has been on this planet for thousands of years. It survived and thrived while people commonly ate certain things and never ate other things. If our distant ancestors made it through childbirth and dodged infectious diseases and predators, they seemed to stay healthy and live robustly into old age. Only with the introduction of grains, sugars, and other starches as a large part of our daily diet did we begin to get fat and sick (with chronic noninfectious diseases). I memorized *The Primal Blueprint* and tried to live by it as best I could. I lost another 20 pounds and started having fun and enjoying life again. I didn't feel the need to work out anymore; I would just go outside and play like a kid. I was going through family and social changes, yet they didn't get me down and make me angry like they would have when I was fat. It was almost as if changing my diet had changed my mood, attitude, and outlook as well.

Since then, I have read many more books about human nutrition, including *The Paleo Diet*, *The Paleo Solution*, and *The Bulletproof Diet*. My diet and lifestyle are a blend of all those concepts. Currently, I'm investigating intermittent fasting, thermogenics, and optimization of my gut bacteria as ways to further improve my health and mood. When I find something that works and is safe, I share it with my patients. So, you see, doctors can wake up and get out of their little boxes if they try. You might even be able to wake up your doctor.

So, what's wrong with your doctor? Let me first reassure you that your doctor is probably a well-meaning, thoughtful, and caring person who wants the best for you. All doctors start out this way. Although these traits get buried and sometimes become dormant, I'm sure they're still in there somewhere. Doctors are very, very busy people. There are pressures and expectations on them that you might not imagine. There are hundreds of

pages of medical journals to read weekly and thousands of pages of government/insurance regulation updates to read monthly—not to mention a practice (small business) to run, social expectations to manage, and family to spend time with.



I don't say this to make excuses for your doctor. I say this to remind you that your doctor is human. He has only so much time, effort, and brains to go around. Unfortunately, it's human nature to look for shortcuts when you're overstretched, overstressed, and overpromised. Let me describe for you some of the shortcuts your doctor might be taking that could affect your health. Keep in mind that your doctor takes these shortcuts not because he's mean, dishonest, or part of some conspiracy. He does it because there are only so many hours in a day, and he can't do everything.

THE LAWS OF HUMAN NATURE THAT APPLY TO YOUR DOCTOR

Doctors are human (at least for now), and as such, they are just as liable to fall victim to errors of thinking, of taking shortcuts, and of being, well ... human as any of the rest of us. This is why my first chapter reminded you to have faith in God but not your doctor. Doctors are on average very smart people, but that doesn't make them infallible or above suspicion. Just ask any state medical board. Medical boards are suspicious of all doctors, especially those who step outside the box or dare to try something new. Here are a few thought-errors your doctor probably falls victim to.

When the only tool you have is a hammer, everything looks like a nail.

This is an important law of human nature. You should understand this idea as it relates to your doctor, your mechanic, and every other expert in your life. Abraham Maslow and others describe this idea as the *law of the instrument*. Maslow noted that if you give a young child a hammer, then the child will hammer everything that's within the child's reach. Let me explain how this applies to your doctor: We all understand what a hammer is and what it does to a nail. However, you should consider that tools not only help us do work but also affect the way we think about the work we do. As a result, the tools we have available can alter how we go about doing our work.

If a carpenter has only a hammer and nails, then he will think about nailing things to whatever he is doing. If all he has is a saw, then he will think about ways of cutting off pieces of what he is working on. This was a great strategy back in the Paleolithic days, when human beings had limited tools. It helped them figure out how to take a stick or a rock (the only tool they might have had) and knock fruit out of a tree, so they didn't starve. Today, however, we have multiple tools at our disposal. Some tools are good, and some are not so good. However, this way of thinking is still hard-wired into our brains. As a result, it can cause us to use the wrong tool. We tend to consider using only the tools we have readily available and the tools we have already learned how to use to get our work done.

Here's an example of how this way of thinking could affect your doctor: A family doctor advising an obese diabetic would probably say that the patient needs to cut back on calories, eat less fat and more whole grains, and exercise more. The doctor might also prescribe a daily pill or three to take. The *tools* this doctor has easy access to are the nutrition *facts* he learned in medical school and his prescription pad. He's too busy to learn about other tools that he could use to help this patient. Therefore, the patient gets the benefit of only the tools his doctor knows about and chooses to use. A surgeon advising that same obese diabetic might say that the patient needs stomach-bypass surgery to cure his diabetes and obesity. The tool of a surgeon is surgery, so that is what the surgeon tells the patient he needs. An endocrinologist (a doctor who specializes in glands and diabetes) who sees the same patient would probably give the patient an insulin pump and a prescription for some of the most expensive medications on the market.

Those are the tools that this expert uses daily, and thus the ones he is proficient at using. All three scenarios involve the same patient, but each expert uses a different *tool* to help the patient. You should be saying, “I wonder if other tools exist that would work better for this patient that weren’t used at all.”

Good thought! Each doctor is using the tools he’s comfortable with. These doctors are neither considering each patient as a unique individual nor are they looking for new (or old) tools that might work better than their current tools. How should we feel about these three doctors? Should we judge them, hate them, praise them, or ignore them? These behaviors don’t make the family doctor, the surgeon, or the endocrinologist bad or dishonest. They just make them human. There are other tools available to help this patient, but these doctors use only the tools they currently know about and believe in. Only a doctor who is constantly reading and learning, and who often does research outside of his specialty or even outside the field of medicine, will discover better tools.

Learning about new tools is time-consuming and full of dead ends. You may invest hours studying some new tool only to find that it doesn’t work, is too expensive, or is just too dangerous to use. Doctors learn to be stingy with their time, and rightfully so. They have only so much time, and some portion of it is already spoken for. Also, as the saying goes, time is money. Time a doctor spends searching for a better tool means less time to use his existing tools to make money. Therefore, you can understand why a doctor might choose not to look for new tools or might ignore a new tool that is unproven or not approved by his medical board, his professional society, or the FDA.

When your income depends on believing a certain thing, you tend to believe it.

Upton Sinclair once wrote, “It is difficult to get a man to understand something when his salary depends upon his not understanding it.” This law of human nature sounds dishonest on its face. However, it doesn’t necessarily mean that your doctor is dishonest. The way the current system is set up, a family doctor will never get in trouble with the state medical board for telling you to eat fewer calories, eat whole grains, eat low-fat, and eat less salt—even though this counseling has been shown in multiple meaningful studies to be terrible advice and to almost never work. His income and his future as a doctor are perfectly safe if he repeats this

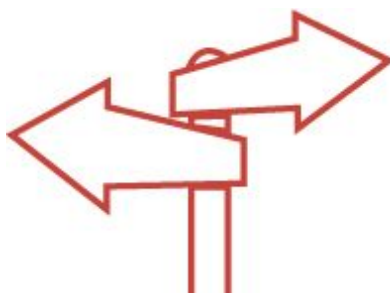
foolishness daily for the rest of his career. This advice helps no one. All his patients end up feeling guilty and give up because it's impossible for them to follow this advice. The surgeon will never get into trouble with the state medical board for performing bariatric surgery, even though his patients can end up with long-term problems and very uncomfortable lives. They can even gain back the weight, assuming they have no devastating surgical complications in the operating room (a signed waiver legally protects the surgeon from these). The endocrinologist is safe with the medical board when he prescribes an insulin pump, even in a patient whose pancreas still makes insulin. He is even safe in prescribing medications so expensive that the patient is guaranteed never to be able to afford them.



Now, let's suppose that a doctor, through thinking, reading, and researching, comes up with a diet plan, pill, or shot that will cure this overweight diabetic patient permanently. What can, and what should, he do with this treatment?

If this good doctor started trying to tell the world about this new tool to cure obesity and diabetes, how would he go about it? In our culture, he would advertise. That is how we spread the word about new discoveries from which other people could benefit. Therefore, this doctor would take out ads in the newspaper, get a website, create a Facebook page, and proceed to

tell the world about this new tool he has discovered. He would proudly proclaim to the world that none of the other tools doctors had told them about were necessary. They need only use his new tool, and their obesity and diabetes would go away so they could be healthy and happy. Can you guess what would happen next? This doctor would quickly receive a not-so-nice letter from his medical board telling him to stop advertising his tool immediately. Even worse, he might even receive a summons from the board with the threat of a fine. The medical board might even take action against his medical license—such as suspending or revoking it—even if his tool does, in fact, work better than every other tool out there. Regardless of whether it's the best tool ever invented to cure obesity and diabetes, the medical board wouldn't care or want to hear about it. I'm telling you a true story, my friends.



Humans (doctors) are always looking for shortcuts in every part of their lives.

We all love shortcuts, and that's one reason we live in a modern society in which we have a machine to do almost every task for us. As discussed previously, one seemingly useful time-saving shortcut that doctors take is to read only the conclusions in the many medical journals they skim; they don't read entire articles. The reason is that most medical studies, when published, are broken into parts, including the abstract, background, methods, and conclusion. Summarizing only the conclusion is also what the news media does when it reports on medical studies with the intent to scare you. Often, when I hear a news report on one of these studies, I have to roll my eyes. It's obvious that someone with no medical training has read only the conclusion or someone else's summary of the conclusion. The conclusions of medical research studies often don't truly represent what the study's results revealed.

Another shortcut that doctors take is to lump patients into several groups. Then, when they encounter an individual patient who seems to fit into one of these groups, the answer to the question of which prescription pill to give is obvious. For this type of doctor, there is no such thing as a unique patient; there are just different types of patients. Thinking is hard work, and if a doctor is a little lazy or a lot overstretched, this shortcut seems well worth it in the short term. Obviously, though, with these shortcuts, the patient is often shortchanged and can even be harmed.

Association seems to imply causation.

Just because there's an association between two things does not mean that one of those things causes the other thing to happen. This concept is hard to understand and to keep in mind. Sometimes it seems that because two things are related, one thing must have caused the other thing. For example, your parents might have told you to stay away from the bad kids because they believed that good kids who hung out with bad kids would become bad kids themselves.

A medical example of this philosophy is the story of HDL cholesterol. Medical studies have shown that having a high HDL ("good") cholesterol level is associated with a lower risk of heart attack. Therefore, it would seem like a good idea to give patients a pill to raise their HDL level. That should decrease their risk of having a heart attack, right? Doctors have tried this, but the subsequent research found that giving someone a pill to raise their HDL level did not lower their risk of heart attack. High HDL and low heart attack rates are related, but raising a person's HDL does not lower his heart attack risk. High HDL levels are associated with a reduced heart attack risk, but they do not *cause* the decreased risk.

Another example is when a parent brings a sick child with a runny nose and a cough to the doctor. He prescribes the child a course of antibiotics, and a few days later, the child is feeling much better. It appears to the parent that the antibiotics cured the child's illness. In fact, the viral infection causing the illness would have improved in the same amount of time without the antibiotics. Even though the antibiotics seemed associated with the cure, they did not cause the cure.

There once was a study showing that swimming pool drownings were associated with the number of Nicholas Cage movies released during that same time. Even though there was an association between these two things,

you would have to be a little unstable to think the drownings were Mr. Cage's fault. The numbers were just a coincidence. In this example, it's easy to see that the two variables (drownings and Cage movies) can't possibly be related. However, in medicine, it's sometimes much harder to tell (HDL levels and heart attack rates).

I would love it if every person on the planet understood this error in thinking, but I don't expect that to happen. I do expect every doctor in medical practice to understand this concept completely and never to be fooled by it. That's a reasonable expectation because most doctors learn about this error in thinking early in their training. However, I'd say that they're not taught well enough; it's one of the most common errors I see doctors make. Still, I do expect every doctor to see through Big Pharma's advertising, which sometimes craftily exploits this error, and not subject their patients to unnecessary pills because of those misleading ads.

When something *sounds* true, we often start believing that it *is* true.

We've all heard the story about George Washington chopping down the cherry tree, but it's an historical lie. Sometimes, when a lie sounds like it should be true and people repeat it often enough, even experts in the field begin to believe the lie and repeat it. Even doctors do this. Just as many teachers through the decades have *taught* their students the lie about George and his naughty hatchet, doctors sometimes *teach* their patients medical lies that are harmful. When we learn a medical lie from a doctor, it can affect our health in negative ways.

Medical lies don't usually start this way, but it is how a few of them have been born. The problem is that when an expert tells a medical lie—whether it's your doctor, the ADA, the FDA, the AMA, or the USDA—patients tend to believe it blindly. The patients then repeat it and keep repeating it for years, even after the experts have disproved it and stop repeating it themselves. Experts very seldom (and by “seldom” I mean *never*) retract their previous opinions in a meaningful public way when they've been proven wrong by further research. The experts just stop repeating the lie and move on with their careers as if nothing had happened. You, as a patient, would have no way of discovering this change in expert opinion without doing hours of research on your own. Therefore, you continue to believe the lie. This is what I call the *echo of the lie*.

A lie keeps echoing through society even after it has been proven false.

When researchers realize that what they'd been publishing as truth in their studies is false, they don't issue a press release to apologize and ask everyone to forgive them for the error. They just stop repeating the lie and move on to the next thing. It's a huge nonevent. They don't want to admit publicly that they were wrong, and no one makes them, so they don't. For example, where are all the doctors pleading for forgiveness on bended knee because they told us for years that we shouldn't eat butter? They're nowhere to be found. They've already moved on to other medical topics while leaving the rest of us confused about what happened. You'll never read a published retraction, a public apology, or even a good explanation about where they went wrong, and you'll never receive a promise that they'll never do it again.



They just moved on, which is understandable because no one wants to admit they were wrong. However, because the perpetrators of the lie are experts, they're causing harm by not correcting the lie. The lie continues to echo through society, sometimes for decades, continuing to harm or inconvenience patients. For example, even after researchers quietly backed away from the eggs-are-bad-for-you lie, it kept being repeated by the media and doctors for years. When the scientists and most of the media (but not all) had stopped telling this lie, it was still repeated by primary care doctors, spouses, parents, and know-it-all neighbors for many more years. To this day, I still have the occasional patient who will argue with me that eggs are full of cholesterol and bad, so they shouldn't eat them. When I tell them to stop eating cereal and milk for breakfast and to eat eggs instead, they look confused and mutter, "But I thought eggs were bad?" This question makes me want to climb a few ivory towers and slap some experts (figuratively, of

course). The researchers should have made as big a deal, and just as big a press release, of revealing to the world that their original conclusions about eggs were wrong as they did when they made the original incorrect announcement. If the experts were searching for truth rather than recognition, they would have willingly advertised the change in opinion.

If something is less bad, then it must be good.

Two arguments I deal with in more detail later in this book are that whole wheat is better for you than processed wheat, and raw milk is better for you than processed milk in a carton. When I present the research on these two arguments, you will see that, in fact, whole-wheat foods are less bad for you than processed-wheat foods. In the same way, raw milk (properly collected and stored) is less bad for you than processed milk. However, just because something is less bad for you does not mean that it's good for you. Less bad *does not* equal good. This is an error in thinking that doctors make all the time.

If we did a medical study comparing the health effects of smoking unfiltered cigarettes versus smoking filtered cigarettes, what do you think we would find? Of course, filtered cigarettes (assuming the filter is made of something safe) should cause less disease than unfiltered cigarettes. You, as the researcher, would publish your results in a medical journal with a title such as "Filtered Cigarette Usage Leads to 15.3% Fewer Lung Cancers," and you would feel like you had made the world a better place. A news outlet or government agency publishes a story about your interesting little article, and their story is titled "Filtered Cigarettes Are Much Healthier than Unfiltered." Finally, the local news stations, smaller websites, and parents everywhere tell the world, "Filtered cigarettes are good for you!" Do you see what happened there? In your research, you never meant to claim that filtered cigarettes were actually *good* for people. You were just studying two variables and reporting your findings. Sadly, once your findings had filtered down through doctors, the government, and the media, they had been turned into a lie. This sort of transformation happens all the time in medical research, and it's your doctor's job to detect it and protect you from it.



Mindless repetition of a lie makes people believe it.

When your neighbor, Bob, tells you something like, “Trust me; the more you exercise, the more weight you will lose,” he’s not breaking any rules. Regular people get to say whatever they want, whether they know what they’re talking about or not. You can’t hold Bob liable for this error, and you can’t sue him for damages. He was just stating his opinion on the matter. If your hairdresser tells you, “Honey, you shouldn’t eat seeds and popcorn; it will flare up your diverticulitis!” then it is up to you to decide how much she learned about the human colon in her cosmetology classes. She isn’t an expert in the medical field, and she doesn’t have to be right, or even try to be right, when she shares information. Both Bob and your hairdresser are repeating things they’ve heard, things that sound correct to them, so they then pass these little nuggets along to you and everyone else who will listen.

For regular folks, this behavior is perfectly acceptable. You shouldn’t be surprised if they’re often wrong. Doctors, however, should be held to a higher standard. They should either be certain that they know the right information or realize that they might not know and tell you as much. When doctors repeat medical lies, people do get hurt, and the doctor can be held responsible.

When your doctor mindlessly repeats something he read in a medical journal or something he was taught in medical school twenty-five years ago without thinking about you as a unique patient, he’s doing you a great disservice. He should be held accountable for his lack of effort. He is neither your neighbor nor is he your chatty hairdresser; he’s a licensed expert in human health who’s tasked with the responsibility of giving you the best medical advice available. You have every right to expect that your doctor knows what he’s talking about when he speaks. Your doctor, as a licensed

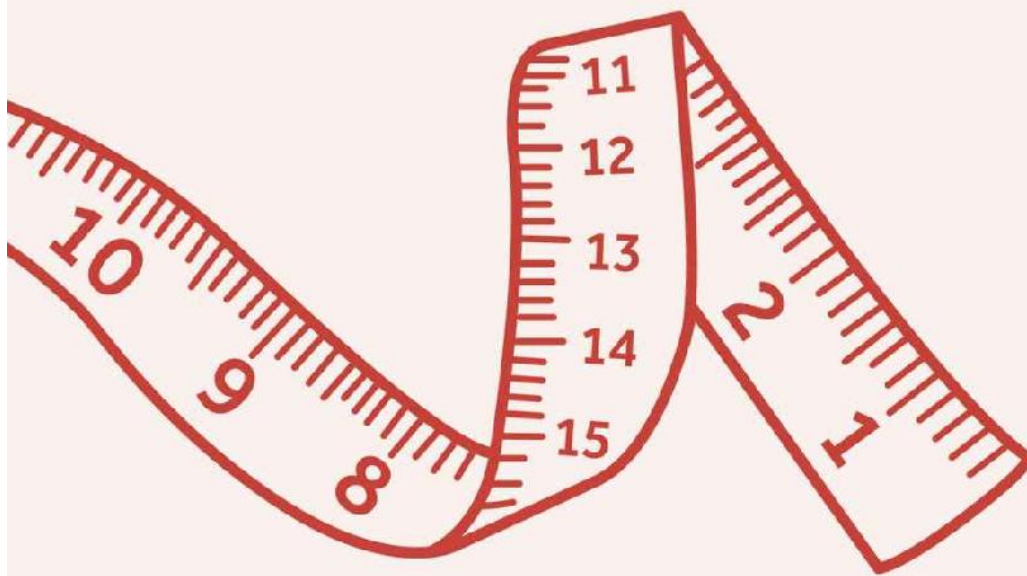
expert, doesn't have the lazy luxury of repeating something without knowing if it's true. He has a sworn duty to read the medical journals and the relevant studies (in their entirety, not just the conclusions), and even to read outside the field of medicine. Doing so will help him see the bigger picture concerning the health and well-being of his patients. It will also keep him from mindlessly repeating the latest guidelines from Big Government or Big Pharma without stopping to think whether they are based in meaningful research.

When doctors fail us in this most basic area of trust, they also lose credibility in other areas. A doctor should willingly tell his patient when he doesn't know something if that is the case, and he should say that he'll research the issue and report back when he does know. Patients should be able to trust their doctors to be intellectually honest. They aren't paying for good-sounding random answers to their medical questions. They deserve well-thought-out, researched answers that apply to their unique cases. This tendency to perpetuate medical lies is the reason, above all others, I wrote this book. Patients deserve a doctor who will either know the answer, find out the answer, or refer them to a specialist. A patient never deserves a thoughtless canned answer that might or might not be true. A doctor should never repeat a medical lie he has heard or read to his patient, call it medical advice, and be held blameless for it. Those days are over.



Chapter 3

THE SKINNY ON FAT



Unless we put medical freedom in the Constitution, the time will come when medicine will organize itself into an undercover dictatorship. To restrict the art of healing to doctors and deny equal privileges to others will constitute the Bastille of medical science. All such laws are UN-American and despotic.

—Benjamin Rush



THE LIE

Eating fat, especially saturated fat, leads to high cholesterol, obesity, and heart disease.

WHY YOU SHOULD CARE

If fat in our diet does lead to high cholesterol, obesity, and heart disease, then we should avoid it at all costs. If, however, this tasty food has been falsely accused, then wouldn't you like to enjoy it at your liberty? If it's good for you, then wouldn't you want to eat more fat, not less? This important question in the fields of nutrition and medicine needs to be answered with meaningful research and common sense.

SUPPORT FOR THE LIE

All experts, federal government agencies, and academies eagerly repeat this medical lie. It seems so self-evident to the well-meaning experts that dietary fat equals body fat that there is little need for actual thought or research on this subject. If you look for the actual hard research, however, you'll find very little support for this lie. Multiple large studies over the years, which were conducted to show once and for all that eating fat was bad for you, have repeatedly shown no link between fat consumption and increased risk of heart attack or stroke.

THE COMMON SENSE

In few areas of human health and nutrition have medical scientists been more completely and embarrassingly derelict than on the topic of fat nutrition. Something as basic as what human beings should eat to be healthy is still a mystery in the twenty-first century. Or is it? Experts would have us believe that we need to fill up on whole grains and wash them down with glasses of skim milk and fruit juice. These same experts tell us that we should turn away from all saturated fats. However, the evidence for this advice is lacking.

Common sense is defined by Webster.com as "sound and prudent judgment based on a simple perception of the situation or facts." What sense could be more common than thinking we should follow the same diet and behavior that our ancestors followed for thousands of years? These hardy

ancestors of ours were hunter-gatherers and didn't stay in one place long enough to grow and genetically modify grains or grasses. They moved around and ate what they could get their hands on. They probably wouldn't have touched skim milk, had it been a choice. They went out of their way to eat fat, breaking open bones for marrow and skulls for brains.

The DNA you carry in every cell of your body was formed and perfected in the harsh environment that was your ancestors' lives. For thousands of years, that DNA was tweaked and perfected on certain foods, green things, protein, and fat, but it never encountered other foods (grains, fruit juice, and skim milk). Therefore, the true commonsense thinking on this topic would be to honor your DNA and eat as much like your ancestors as is practical and possible. Unfortunately, most of us don't do this because the experts stepped in a few decades ago and lied to us.

A *pseudo-commonsense* idea has hijacked this topic: Because the fat in foods and the adipose tissue on our bodies are called by the same word (fat), most people (and most doctors) childishly assume they are the same. As a result, the assumption is that eating one fat, in your food, must lead directly to the production of the other fat, in your body. Although this logic might satisfy a yearning for symmetry and simple arithmetic in the mind of the average person, we should justifiably expect a much higher standard from our nutrition experts and doctors. It's neither their lot nor their privilege to accept anything blindly as fact without rigorous study and trial, even if it sounds like perfect common sense. The job of doctors is to think and to study and to prove or disprove what they and everyone else thinks they know to be true.



With regard to this medical lie, and several others, doctors have let their patients down and embarrassed themselves by continuing to claim that they're experts on the subject. Many a patient has been deprived of the taste

and nourishment of the fats our ancestors enjoyed because a well-intentioned doctor or dietitian said it was bad for them. People have been made to feel guilty and selfish for eating the very foods their DNA craves. Our DNA knows exactly what we need, and ignoring it leads to obesity, disease, and early death.

Let's turn to the farm for some common sense. When a farmer wants to fatten up a cow or pig, what does he feed it? Bacon, butter, and egg yolks, right? That would make perfect sense based on what doctors tell us to avoid when we're trying to lose weight. Umm, no, that wouldn't work at all. It would be very expensive, and the farmer's animals would become leaner, not fatter. When a farmer wants to fatten up livestock as quickly and cheaply as possible, he feeds them starches and carbohydrates as aggressively as the animal can stand it. The feed is usually a combination of corn and grain. If a doctor went to the farm and told the farmer that feeding his cows whole grains and corn would be a great way to help the cows lower their cholesterol and lose weight, he would be justifiably laughed off the farm.

When a farmer wants to cause a goose's liver to become as fatty as possible (pâté is made from the fatty livers of geese), he force-feeds the goose lard and tallow, right? Apparently, that's what a doctor would recommend to the farmer. No, the farmer force-feeds corn to the goose with a plastic tube, a not-very-nice process known as *gavage*. If your doctor has told you that you're developing fatty liver disease because you've been eating too much fat, I hope you're starting to see the silliness of this lie. To fatten up any animal, you feed it large amounts of corn and grain, but somehow, magically, you fatten up humans by feeding them fat? That "logic" doesn't make sense.

THE RESEARCH

You would expect, given how often this medical lie has been and is repeated, that there must be hundreds of medical studies showing beyond all doubt that eating fat makes you fat. In fact, there are no studies showing this to be the case, and there are multiple large studies showing the exact opposite to be true. We expect doctors and experts to think about and study everything, but they don't. Doctors ought to question everything and believe nothing until it has been proven by meaningful medical research. However, when we remember that busy doctors are human, it's understandable that they have believed this medical lie and repeated it because it seemed so self-evident

and had been championed by every leading medical authority. It just didn't seem worth the time and study needed to prove or disprove it.

This lie originally gained real traction with the publication of the Seven Countries Study by Dr. Ancel Keys, who started collecting data in 1956 in Yugoslavia and finally published his study in 1978. The deeply flawed (some would say dishonest) study appeared to show that eating saturated fat was linked to rising cholesterol levels in the blood, which would then lead to heart disease. Dr. Keys collected data from twenty-two different countries, but when he published the study, it mysteriously contained data from only seven of those countries, hence its name. Are you wondering why Dr. Keys didn't publish his data from all twenty-two countries? Can you guess? The reason, I kid you not, was because the data from the other countries showed that eating fat either had no effect on the rate of heart disease or actually protected the eater from heart disease. So, the data from those countries was intentionally left out, and suddenly every expert, even the federal government, was telling us that saturated fat had been proven bad for our hearts.

Why did the government get involved, you ask? Dr. Keys had received grants of \$200,000 a year from the U.S. Public Health Service. Evidently, they needed to show some results after spending all that money. It quickly became clear to doctors in the United States that unless they wanted to be laughed at, left behind, or worse, they had better climb on board the eat-low-fat, cholesterol-is-bad train. Researchers on the subject began accepting the Seven Countries Study as fact and started doing research—not to retest Dr. Keys's theory but to prove subtheories that were all tainted with the assumption that the Seven Countries Study was proven truth. These studies did some suspect things, like lumping saturated fats and trans fats into the same category, which is an obvious flaw that provides meaningless conclusions when it comes to human nutrition. Trans fats (such as margarine and shortening) are most certainly bad for your health. Lumping them in with saturated fats tainted the research and made the conclusions misleading and dishonest. Only in recent years has more honest research been conducted and published. I discuss Dr. Keys and his study in more detail in [Chapter 5](#).



THE TAKE-HOME

Medical science and doctors are sometimes wrong. Thankfully, they're usually just a little wrong, not completely wrong. However, in this case, it looks like doctors were (and for the most part still are) completely wrong. They're giving you exactly the wrong advice on the subject of nutrition, fat, and health. Telling you to cut down the amount of saturated fat you eat as a way of losing weight and avoiding heart disease won't have the effect most doctors expect. It will remove many tasty things from your diet but result in no meaningful weight loss or decrease in heart disease risk. With the obesity epidemic in our culture, we need to focus on dietary and lifestyle changes that lead to real improvements in our weight and waistlines. Dr. Keys must be taken down from his demigod status and recognized for what he was.

He was someone who wanted to do great things and help humankind. He was also a man who made a horrendous mistake that then became one of the biggest medical lies of all time. He cherry-picked the data he would publish in his flawed study, and he evidently didn't have the courage to admit that his research findings were flawed and had disproved his hypothesis. Most other experts at the time accepted his study without the critical thought they were duty-bound to apply to it, and they parroted his misleading results to the world. The pharmaceutical industry smelled a few billion dollars to be made and jumped into the research wholeheartedly. We shouldn't be surprised that every research study paid for by Big Pharma has found that more and more people should take cholesterol pills and eat less fat. The companies' continued financial success depended on proving this.

Your brain and nerves are made largely of fat and cholesterol. Without the fat in our cell membranes, life as we know it wouldn't be possible, neither would the signaling that occurs between the cells that make up our bodies. We have known this to be medical fact for decades, so I'm still unclear as to why Dr. Keys's study had the huge effect it did on doctors and medical practice. Even to this day, for a doctor to suggest that eating fat is anything but bad is shocking to most people, and especially to most other doctors. When I tell patients that eating fat won't make them fat, as I routinely do, the usual expression is one of shock or disbelief. (*Wait, what did he just say?*) Never in their lives have they heard that phrase before. It flies in the face of every shred of nutritional advice they've ever received from their doctors, their neighbors, and their parents.

I tell them to go home, look in the mirror, and repeat ten times, "Eating fat won't make me fat, but eating sugars and starches will." Usually, that helps them begin to wrap their heads around this new way of thinking. It also allows them to start to think logically about diet and weight loss. Our ancestors never left behind available fat. It was usually the first thing they ate. We should copy their behavior and honor our DNA by eating good fats often.

A hundred years ago, everyone cooked with animal fats like lard and tallow. At that time, heart attacks were unheard of in patients younger than seventy. Obesity was very rare. I often ask patients in their seventies and eighties how many fat kids were in their first-grade class. The answer is always either one or none. Now that we cook everything in vegetable/seed oils and lard is a dirty word, childhood obesity is rampant, and heart attack and stroke are the leading causes of death. It's becoming all too common for people to have their first heart attack in their forties or fifties. Go to the average first-grade class these days and look at the kids who've never eaten anything cooked in lard. Forty percent of children are obese. You think there might be a connection? Here is a hint: A researcher went back over *all* of Dr. Keys's research and found that sugar consumption was much more correlated to heart disease than fat consumption, which means that sugar consumption was much more likely to be the cause of heart disease than fat consumption. The relationship between sugar consumption and heart disease risk existed in all twenty-two countries, not just the seven countries Dr. Keys included in his publication.

If your doctor tells you that the key to losing weight is to eat less fat and exercise more, get up, politely walk out of the interview, and find another doctor. There is probably no hope for him. This one statement, perhaps more than any other a doctor can make, tells you all you need to know about how current this doctor is with his reading and how active he is with his thinking. *Eating fat makes you fat* is the statement of a lazy, unthinking doctor. It's not the statement of someone who has done the work to stay current to be able to give you the correct advice. There are regular individuals who make YouTube videos with better nutrition advice than you can get in the average doctor's office. Doctors have ignored good diet and proper nutrition, both vital to health and long life, for too long. If your doctor doesn't give you real, useful diet and nutrition advice, then get it elsewhere.

DO AS I DO

I include plenty of fat in my diet. Sometimes I eat so much fat that it freaks out my lunch partners. I have found that eating fat to my heart's content helps keep my weight under control and my lab results within normal limits. My body seems to love fat, and it runs much better on fat as fuel. I put grass-fed butter in my coffee and on almost everything else. Egg yolks are now my favorite part of the egg (back in my fat-assed, dumb-doctor days, I would eat only the whites). Bacon is no longer a stranger to my plate.

HOMEWORK

There is so much good information about how healthy good-fat-consumption is that I'm recommending three books, not just two. After reading these books, you will be as smart as any doctor when it comes to the health consequences of eating good fats.

Book: *Eat the Yolks* by Liz Wolfe, NTP (2014)

This entertaining book explains in plain words the somewhat complicated story of how fat and cholesterol became dirty words in modern medicine.

Book: *The Big Fat Surprise: Why Butter, Meat & Cheese Belong in a Healthy Diet* by Nina Teicholz, MA (2014)

This excellent book is full of studies, citations, and common sense that destroy the myths that red meat, fat, and cholesterol are bad for humans in any way.

Book: *Eat Fat, Get Thin: Why the Fat We Eat Is the Key to Sustained Weight Loss and Vibrant Health* by Mark Hyman, MD (2016)

One of the few doctors in the know, Dr. Hyman explains all the ways that eating fat is good for you.



Chapter 4

YOUR BONES DESERVE BETTER



**The reason doctors are
so dangerous is that they
believe in what they
are doing.**

—Robert Mendelsohn



THE LIE

Drinking milk is good for you and helps keep your bones strong.

WHY YOU SHOULD CARE

You want to eat and drink only what is good for you. If milk is indeed healthy and good for your bones, then drink up. If it is not healthy—but is bad for your bones, as some studies show—then you should avoid it.

SUPPORT FOR THE LIE

Virtually no research shows that drinking milk strengthens human bones, and there is no research showing a society that consumes dairy on a regular basis has stronger bones or is healthier than one that does not. Without research to back up the health claims for dairy, the mega-corporations producing it spend millions of dollars making slick commercials and ad campaigns (“Got Milk?”) to trick you into thinking milk is popular and good for you. Now that dairy farms are big business, we can no longer trust what they tell us about their product.

THE COMMON SENSE

Baby mammals are born small and helpless. To survive, they must grow and gain weight as quickly as possible. The milk of mammals is meant to do one thing very well; it is meant to help infant mammals of that species grow and gain weight quickly. Human beings are the only mammals on the planet who drink milk as adults. No other adult animal does this, unless we humans give it to them. As soon as nonhuman mammals are mature enough to catch and digest other food, they stop drinking their mothers’ milk.

If drinking milk in adulthood were truly healthy, then you would think at least one other species on the planet would do it. There would be some sneaky weasel who would steal into the nest of another mammal so it could nurse the nutritious milk from its new mommy. But there is no such animal, even though animals will trick and mimic to get almost every other form of nutritional advantage. The common sense of this lie takes us back to the truism that just because something tastes good doesn’t mean you should eat or drink it. I tell patients all the time that I hear crack cocaine is amazingly

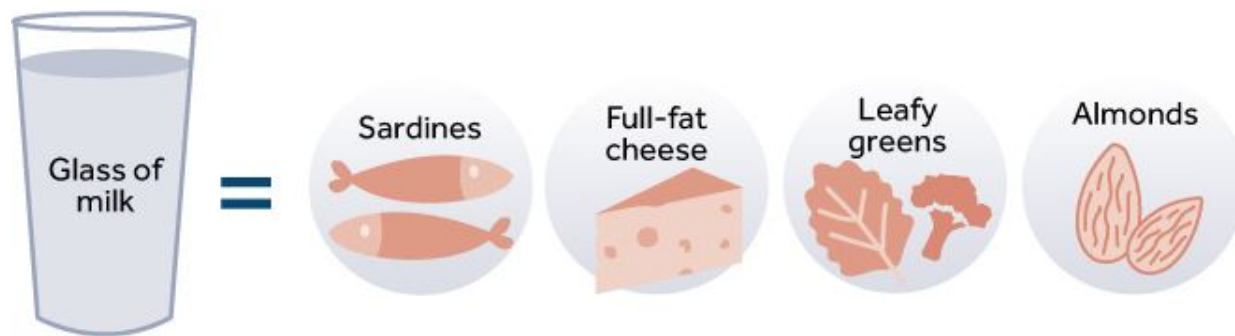
pleasurable, but that doesn't mean we should run out and try it. This statement usually gets a chuckle, as well as a look of understanding.

Milk is the perfect food for babies of the same species as the source that's providing it but is only a tolerably good food for baby mammals of other species. It is well known that milk from different species has different percentages of fat, protein, and other nutrients uniquely tweaked to be the perfect food for babies of that species. Milk from cows is ideally suited as food for young calves but is not a great food for humans. There are much better sources of nutrition for adult humans than milk from another animal.

THE RESEARCH

Recent research shows that drinking milk can weaken bones rather than strengthening them. The countries with the highest dairy consumption have the highest rates of osteoporosis. Countries whose populations drink the most milk have higher rates of hip fractures as they age than countries whose populations drink much less milk. Read those two sentences again and let them sink in.

Studies show we get plenty of calcium from our diet if we eat lots of organic whole foods. Leafy green vegetables are excellent sources of absorbable calcium. They do not have the inflammatory sugars and proteins contained in milk or the other chemicals that are added to milk (either accidentally or on purpose).



Most of the time, when the calcium contents of two different foods are compared, they are listed by the cup, which can be misleading. A much better way to compare the calcium levels in different foods is to compare them by the calorie. When compared to 100 calories' worth of other foods, 100 calories' worth of milk is revealed to be a very poor source of calcium. In addition, only about one-third of the calcium in milk is absorbable by the

human body; the remainder is filtered from your blood by your kidneys and excreted in your urine.

Research is beginning to show that we don't need as much daily calcium as was once believed. An excess of calcium can lead to other problems, including heart artery disease (but not kidney stones!). Cow's milk available in stores does not naturally contain useful amounts of vitamin D; it is added to the milk during processing. The amount of vitamin D added to the milk you find in the grocery is only enough to keep humans from developing rickets. It's not nearly enough to optimize bone and hormonal health. Thus, milk is also a very poor source of vitamin D.

THE TAKE-HOME

When I was a high school student and playing basketball and football, I would drink almost a gallon of milk every day. My teenager brain just knew that this had to be healthy and would make me be a better athlete. I was a decent athlete during my high school years, but I doubt the milk had much to do with it. However, the milk likely had something to do with the chronic allergies, dandruff, and acne I suffered. I could have made much better choices, but I was a high school kid and didn't know much. The television commercials that promoted milk had brainwashed my entire family. The billion-dollar dairy industry spends millions promoting ads on TV and in magazines and millions more lobbying the federal government to make sure that the USDA keeps milk in its misleading MyPlate model (www.choosemyplate.gov/MyPlate).

I think milk is delicious. I would drink it if I could find any research or reasons to convince me that it's healthy, but no meaningful research shows that dairy products are healthy daily choices for food or drink. I often tell my patients that if you are going to drink a dairy product, then please drink heavy (whipping) cream. It has much less milk sugar and fewer of the inflammatory proteins, casein, and whey. The worst dairy choice of all is skim milk. With all the fat removed, skim milk is an unsatisfying, high-sugar/inflammatory-protein drink that serves no nutritional purpose whatsoever—unless you want to gain weight quickly. The fat in milk is not the culprit of weight gain, as most people and doctors believe. The real culprits are the sugar and inflammatory proteins in the milk.

Today's milk is a heavily processed food. It has been pasteurized and homogenized to the point that it no longer resembles its original self, except

for being white. There are multiple problems with the milk production process, which are the subject of numerous books and documentaries. The people with the strongest bones in the world just *don't* drink milk. One large study found that women who drink two to three glasses of milk daily have a higher fracture risk than women who drink less than one glass a day. Another study found that men who drink two or more glasses of milk daily had higher rates of prostate cancer than men who drink less milk. The list goes on and on.

I find it sad that most doctors only halfheartedly encourage mothers to breastfeed their infants the perfect milk that's made for infant humans but wholeheartedly bully the same mother into giving that same child multiple daily servings of cow's milk in later years. You can barely find a doctor who will take a firm, vocal stand saying breast milk is the perfect food for infants and is infinitely better than formula. However, you can line up doctors around the block who tell you that cow's milk is a great food for us at any age, which is another example of the upside-down circus called modern medicine.

There is an argument to be made that raw, organic milk from cows, goats, and other animals might be a healthier food for adults to drink than processed cow's milk. Although organic and unprocessed, these milks are still a concentrated source of milk sugars and proteins. This is an example of assuming that something that's less bad for you is the same as something that's good for you.



My concern with drinking milk as an adult is threefold.

As I mentioned earlier, if drinking milk as an adult mammal was a smart strategy, you would think other species would have discovered this good source of nutrition in all the thousands of years we've been on this

planet. Animals are expert at adapting to things that increase their chances of survival, so you'd think some species would have made use of another animal's milk if it were such a great idea.

Many people are lactose intolerant and can't drink milk at all, so obviously it is bad for them.

Even people who don't suffer from lactose intolerance often have allergic symptoms after drinking milk. I suffered from severe chronic allergies until I stopped drinking milk. Now I never have allergic reactions. I've had multiple patients who suffered from allergies, acid reflux, or acne report that their symptoms improved after they've stopped drinking milk.

There have been times in human history when nutrition was very scarce. During those times, drinking milk was a better alternative than starving. The nutrition in milk has kept many people alive during times of famine. However, in today's time of plenty (at least in most of the Western world), there are much better sources of nutrition than milk. If you love milk and your body can tolerate it, then enjoy it occasionally as a treat. But you should no longer be deluded into thinking that processed milk is a health food. It's not good for your bones or any other part of you. Milk does not do a body good.

DO AS I DO

Drinking milk is a thing of the past for me. I avoid all liquid dairy and would never touch skim milk. I put heavy cream in my coffee, but I never use lower-fat versions of liquid dairy. My weight and mental clarity are much better because I avoid liquid dairy. The dandruff, allergies, and acid reflux I suffered in the past are gone now that I avoid milk. As a result, I will never drink milk again. I get plenty of calcium from the leafy greens and fish that I eat. Because I don't live near the equator and I work mostly indoors, I take a daily vitamin D supplement.

HOMEWORK

The paradigm that milk does a body good is so deeply mired in the subconscious of most doctors and patients that you should probably do a little more reading on the subject if you're still undecided.

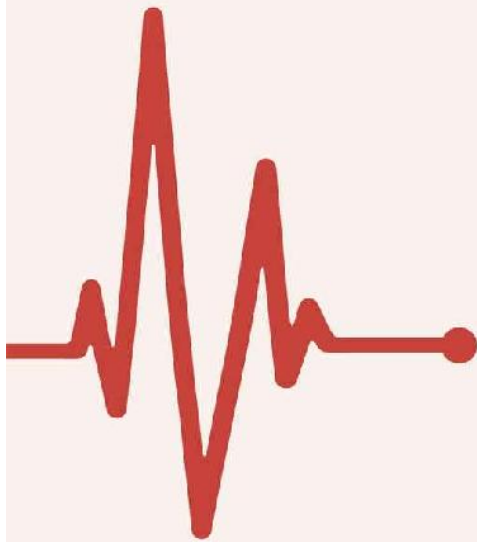
Book: *Whitewash: The Disturbing Truth About Cow's Milk and Your Health* by Joseph Keon and John Robbins (2010)

This book takes a truthful look at how milk is produced and how our bodies react to it. There are also several documentaries on the Internet about Big Dairy and its questionable practices.



Chapter 5

IS CHOLESTEROL REALLY YOUR ENEMY?



**It doesn't matter how
beautiful your theory is,
it doesn't matter how
smart you are.
If it doesn't agree with
experiment, it's wrong.**

—Richard Feynman



THE LIE

High cholesterol levels in your blood are dangerous and increase your risk of heart attack. You should eat less saturated fat and take cholesterol medicine if your cholesterol level is above normal.

WHY YOU SHOULD CARE

Decreasing the risk of a heart attack should be important to all of us. No one wants to have a heart attack, and we all do whatever it takes to prevent having one. All we need to know is what actually leads to increased risk of heart attacks, and what we need to do to prevent them. If you're taking an expensive, potentially dangerous pill every day to lower your cholesterol and thus prevent a heart attack, you want that pill to do what it's advertised to do, which is to lower your risk of having a heart attack. If, on the other hand, high cholesterol levels don't increase heart attack risk, then let's all shake hands and have some bacon.

SUPPORT FOR THE LIE

Hundreds of research studies, thousands of television commercials, and billions of dollars have been used to convince everyone that high cholesterol is a serious problem for which you need a daily pill (or two). Virtually every expert and organization acts as if this is a no-brainer; they act like you would be a fool not to want to lower your cholesterol. The cholesterol level considered to be normal has been reduced several times over the years. With each decrease, the number of patients who "needed" to take cholesterol medication increased. At one time, doctors considered a total cholesterol level under 300 to be just fine. But then new research (both directly and indirectly funded by Big Pharma) found that level to be much too high and lowered the upper limit of normal to 250, then 240; now we are told that it should be less than 200. Once studies funded by Big Pharma recommend lowering the upper limit of normal low enough, every single human on the planet will meet the criteria for taking a daily cholesterol pill. Obviously, Big Pharma is eager to fund more of these studies.

THE COMMON SENSE

This embarrassing lie, an awful example of medical research and medical science gone wrong, should make patients question every word coming out of their doctors' mouths. Neither common sense nor meaningful research has ever been allowed to play much of a part in this controversial subject.

The common sense concerning this lie is much different from what doctors and the media have taught us. Cholesterol is essential for all animal life. Almost every single cell in your body produces it. Cholesterol makes up at least a third of the cell membrane of every one of your cells. Without cholesterol, none of the cells in your body, including those making up your heart and brain, would function properly. Your body also uses cholesterol as the framework molecule to make vitamin D and all of your sex hormones.

Never so completely has the practice of medicine been hijacked, brainwashed, and made to do the bidding of Big Pharma as when it comes to the cholesterol theory and the medications that lower cholesterol levels. The retelling of this lie is so unbelievable that I won't blame you one bit if you doubt what I say here and must confirm it for yourself. I encourage you to verify the information I tell you about this lie (and all the others).

THE RESEARCH

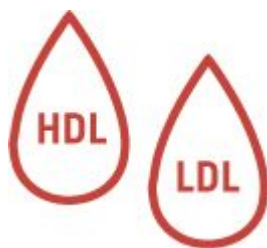
Scientists have known for more than one hundred years that the human body needs fat and cholesterol to create and repair healthy brain and nervous tissue. In fact, each day your body uses cholesterol for hundreds of different repair processes. However, in the 1950s, that fellow I discussed earlier, Ancel Keys, published the Seven Countries Study. Everyone back then respected Dr. Keys as an honest, intelligent expert. Therefore, when his study showed that eating fat and cholesterol raised a person's cholesterol level and increased that person's chance of having a heart attack, everyone believed him. What no one suspected was that this trusted doctor had manipulated the data he collected, either consciously or unconsciously, to show the outcome he desired. He removed the data that contradicted what he was trying to prove.



You'll remember that Keys collected data from twenty-two countries. However, he named it the Seven Countries Study. He simply didn't include the data from the countries that didn't support his theory in his final report. No, I'm not joking. Keys really did that, and the medical community, which evidently was itching for some medical enemy to fight at the time, immediately jumped on the cholesterol-is-bad bandwagon. Butter, eggs, and some meats were vilified based on no research other than this one huge lie told by Dr. Keys.

Some experts disagreed with Dr. Keys and his study findings. However, professional peer pressure and the federal government soon silenced them. Once the cholesterol theory was officially accepted, everyone started trying to cash in on ways to lower patients' cholesterol levels. A great deal of research focused on ways to lower cholesterol. No further research was conducted to confirm Dr. Keys's findings or to try to reproduce them.

In 2015, the USDA Dietary Guidelines Committee Report stated very plainly, "Previously, the Dietary Guidelines for Americans recommended that cholesterol intake be limited to no more than 300 mg/day. The 2015 guidelines will not bring forward this recommendation because available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol, consistent with the conclusions of the AHA/ACC report. Cholesterol is not a nutrient of concern for over-consumption." If your eyes just widened in disbelief, you might want to read that again. *NOT A NUTRIENT OF CONCERN FOR OVER-CONSUMPTION!!!* Has your doctor told you this yet? I sure hope so, but I fear it will be you who must tell him.



A Japanese study published in the *Annals of Nutrition and Metabolism* in 2015 reported that high cholesterol does not lead to heart disease and protects against many illnesses, including cancer. This study found an inverse relationship between all-cause mortality and cholesterol levels. What does that mean? It means that the higher your cholesterol level, the less likely you are to die from any cause. Yes, you read that right. Very low cholesterol levels are associated with an increased risk of dying. As soon as you finish cursing and throwing things, please come back, and I'll explain why you have been told this medical lie so many times by your doctor and media outlets of every kind.

To this day, Dr. Keys's original flawed work is cited in research studies and the media as if it proves anything other than that humans are flawed and imperfect creations, always capable of making mistakes. Most regular doctors have never heard of Ancel Keys and cannot quote from his study. However, they will repeat, parrot-like, his made-up findings as truth and expect you to follow their recommendations. Research has recently shown that elderly people with the highest cholesterol levels have better memories and less dementia than those with lower cholesterol levels. So, could we doctors have been causing higher levels of dementia in elderly patients by lowering their cholesterol levels with medicine?

Only time and research will tell. More and more, research is showing that a high intake of saturated fats (butter, egg yolks, bacon) has little if any negative effect on heart disease rates. I predict we will continue to find that saturated fats in our diet are not negative but are indeed vital to the function of multiple organs and body systems, the most important being the brain and its memory. Most doctors know that the human brain can burn glucose as energy. However, many doctors have forgotten that the brain also can burn selected fats as energy. Some progressive doctors are starting to believe that the dementia epidemic could be at least partially treated or prevented by increasing fat intake among the elderly and perhaps even by stopping elderly patients' cholesterol medicine (statins).

THE TAKE-HOME

In 1961, Dr. Keys appeared on the cover of *Time* magazine. The associated article described how dietary fat had been *proven* to cause high cholesterol, which led to increased rates of heart disease. For the next fifty years, doctors and patients frantically tried to lower cholesterol levels with a pill, or two, or even three.

However, by 2014, butter was on the cover of *Time*. Yes, butter. The accompanying article was about how medical science had gotten everything wrong for decades; fat and cholesterol in your diet have no effect whatsoever on cholesterol levels or heart disease. It took fifty-plus years for enough thoughtful researchers, doctors, and curious laypeople to topple the shrine erected to the cholesterol theory. What was odd about this medical lie (and also awe-inspiring) is that many non-medical people had somehow gotten wise to it before the media had even started talking about it. Alternative medical thinkers and individual patients had out-thought the medical elite. They somehow knew that statin pills were more dangerous than the cholesterol levels these pills were supposed to treat.

When I was still a believer in the cholesterol theory, I remember having patients who were afraid of the side effects of cholesterol-lowering medicines and wouldn't take them. I wasn't sure, at the time, why they felt this way, and I was too arrogant at the time to explore their "foolishness." However, they had it figured out. I would try to get them to at least take a very low-dose statin drug, so they could get some "protection." They would feign being allergic to any cholesterol medicine I started them on. As the years passed and I continued to study, I slowly realized that I was doing my patients no favors by prescribing high-dose statin therapy (the most recommended form of cholesterol-lowering medicine). Consequently, I gradually decreased their statin doses with each scheduled refill.

As many of my patients have transitioned from high-dose statin therapy to very low-dose or no-dose statin therapy, there has been no increase in the rate of heart attack in these patients. However, I certainly have noticed a decrease in their muscle aches and stiffness and an increase in their energy levels. Meanwhile, my colleagues were busy prescribing the highest-dose statin therapy their patients could tolerate, despite the published fact that most patients who have a heart attack have a cholesterol

level of less than 200. My fellow doctors were busy making Lipitor the bestselling drug in history without preventing heart attacks.

Many doctors today, even though they are beginning to understand that the cholesterol theory of heart disease is flawed, are hesitant to stop their patients' statin medications due to fear of lawsuits and/or medical board consequences. It is truly a shame when doctors are afraid to do the right thing for their patients. If you're on a statin, talk to your doctor about slowly decreasing the dosage. Also, please take a daily dose of coenzyme Q10 (200 mg) along with the statin. Taking coenzyme Q10 can reduce the muscle aches associated with taking a statin, and it's very good for your heart health as well. I wouldn't blame you if you decided to stop taking a statin altogether.

If you feel like I'm tiptoeing around just telling you that taking a statin is stupid, that statins do not protect you from heart attack, and that statins might be hurting you, you're correct. I've already felt the wrath of my medical board for recommending natural alternatives to prescription medications, and thus my attorney is a little gun-shy of me running my mouth too much and incurring another fine, or worse.

I predict that one day, history will look back on the cholesterol theory of heart disease and the statin era of medicine with shame and embarrassment. Medical schools will use this period as an example of how research can go wrong and how Big Pharma can influence medical practice for profit. We doctors let our practices, and the care we give our patients, be hijacked by Big Pharma based on flawed research as we were being bluffed and/or stiff-armed by our medical societies and medical boards to comply, or else.

Shameful practices such as this are a large part of the reason that alternative and homeopathic medicine are making inroads and are starting to be accepted by patients as being effective. I can't blame patients for feeling this way and for trying other alternatives. If what your doctor is recommending is silly and perhaps dangerous, then you're justified in looking elsewhere for advice on preventing heart attacks. We doctors can try to blame the drug-makers and the medical journals for this travesty in modern medicine all we want, but we doctors were signing all those prescriptions.

DO AS I DO

I never give a thought to the cholesterol content of any food I eat. I eat as my ancestors would have eaten thousands of years ago and let my body take care of the rest. Although my diet is cholesterol-filled, my cholesterol levels are always within the normal range.



HOMEWORK

The average doctor is far behind on his homework concerning this lie, so you should do a little homework yourself. Read the following books to become an expert on cholesterol and what it means for your health.

Book: *The Great Cholesterol Myth* by Jonny Bowden and Stephen Sinatra, MD (2015)

This book was written by a nutritionist and a cardiologist who teamed up to tease out the truth of this overly complicated subject.

Book: *The Cholesterol Myths: Exposing the Fallacy That Saturated Fat and Cholesterol Cause Heart Disease* by Uffe Ravnskov, MD/PhD (2000)

This book includes good information that will make it easy to understand why you shouldn't fear fat and cholesterol.

Chapter 6

WHEAT ISN'T ALL IT'S CRACKED UP TO BE



**Does history record any
case in which the majority
was right?**

—Robert A. Heinlein



THE LIE

Wheat is a healthy food that is very good for your body. Everyone should eat multiple servings of whole-wheat foods every day.

WHY YOU SHOULD CARE

We all want to be as healthy as possible, and we get this way only if we eat the healthiest foods and live the healthiest lifestyle. If wheat is good for us, then we should eat it all the time. If, however, it isn't good for us, then we should limit how much of it we eat or avoid eating it at all.

SUPPORT FOR THE LIE

Endorsement of wheat as a health food is akin to a religious belief when it comes to governmental and medical experts who make dietary recommendations. From the USDA's Food Pyramid and newer MyPlate models to the newly minted medical student, everyone passionately tells you that you're not eating enough whole wheat. Doctors admit that a few people with celiac disease should not eat wheat, but they think the majority of people thrive on its nourishment. You will be hard-pressed to find a single authoritative committee or organization that doesn't consider wheat a perfect food. We are told that wheat helps in everything from cancer prevention to weight loss, especially products made with 100 percent whole wheat. You would expect volumes of meaningful research to be available on this subject given the experts' wholehearted endorsement of whole wheat, but you will soon find this to be untrue.



THE COMMON SENSE

At first glance, wheat would seem to be just another plant growing from the dirt. Therefore, it should be safe to eat and nourishing to our bodies unless it contains poison, as some plants do. Because wheat is a plant that comes from the earth, common sense suggests that wheat has the stamp of approval. Applying this same thinking to eating other plants, like castor beans and rhubarb leaves, is soon revealed as folly because they both contain poisons that can sicken or even kill you. Just being a plant doesn't automatically make something healthy for humans.

The wheat that bread is made from today is markedly different from the wheat our great-grandparents' bread was made from. As discussed earlier, another commonsense view is that farmers feed wheat, corn, and other grains to the livestock they want to fatten for market rather than feeding them the grass that cows crave or the fat that supposedly makes humans gain weight. If wheat fattens a cow, it probably fattens humans, too.


THE RESEARCH


There are no meaningful research studies showing that eating wheat, either whole or processed, is good for your body. Just because eating a plant causes no obvious short-term problems doesn't mean it's good for your long-term health. There are research studies that show that whole-grain foods are slightly healthier than foods made with bleached flour. Based on these studies, whole-wheat food is recommended as healthy by the average doctor.


This is another example of the thought-error of declaring something is good for you only because it is less bad than something else. The argument that whole wheat is healthier than processed wheat is exactly like the story about the research study comparing unfiltered and filtered cigarettes that I discuss in [Chapter 2](#). Doctors accept and repeat the lie that wheat is great for human health as self-evident without needing further research.

THE TAKE-HOME

Glycemic Index

 Low (less than 15)

 Medium (15 – 39)

 High (40 or higher)

Fruits

| | |
|-----------------------|----|
| Grapefruit (120g) | 25 |
| Apples (120g) | 40 |
| Strawberries (120g) | 40 |
| Bananas (120g) | 47 |
| Peaches, fresh (120g) | 56 |
| Kiwifruit (120g) | 58 |
| Dates (60g) | 62 |
| Watermelon (120g) | 80 |

Vegetables

| | |
|------------------------------|----|
| Spinach (100g) | 15 |
| Carrots, raw (80g) | 35 |
| Tomato soup (250g) | 38 |
| Sweet potato, boiled, (150g) | 61 |
| Pumpkin (80g) | 66 |
| Potato, mashed (150g) | 83 |

Nuts and Legumes

| | |
|------------------------|----|
| Cashews (50g) | 25 |
| Kidney beans (150g) | 29 |
| Black beans (150g) | 30 |
| Butter beans (150g) | 36 |
| Lentils, canned (150g) | 42 |
| Split pea soup (250g) | 60 |
| Black bean soup (250g) | 64 |
| Broad beans (80g) | 79 |

Snacks and Sweets



| | |
|------------------------|----|
| Hummus (30g) | 6 |
| Corn chips (50g) | 42 |
| Snickers (60g) | 43 |
| Blueberry muffin (60g) | 50 |
| Honey, pure (25g) | 58 |
| Sugar, table (25g) | 65 |
| French fries (150g) | 75 |
| Doughnuts, cake (47g) | 76 |
| Pretzels (30g) | 83 |

Grains, Breads, and Cereals



| | |
|------------------------|----|
| Barley (150g) | 22 |
| Chickpeas (150g) | 36 |
| Bran cereal (30g) | 43 |
| Instant noodles (180g) | 52 |
| Taco shells (20g) | 68 |
| Bagel, white (70g) | 69 |
| White bread (30g) | 70 |
| Waffles (35g) | 76 |
| Corn flakes (30g) | 79 |

Dairy and Dairy Alternatives



| | |
|--------------------------------------|-----|
| Skim milk (250g) | 32 |
| Soy milk (250g) | 43 |
| Tofu, frozen dessert, nondairy (50g) | 115 |

Meat



| | |
|---------|---|
| Beef | 0 |
| Chicken | 0 |
| Fish | 0 |

The *glycemic index* of bread, whether whole wheat or not, is higher than that of table sugar. This means that eating two slices of bread will make your blood sugar increase faster than eating a spoonful of pure sugar. This fact alone should make everyone reconsider how healthy wheat is. Glucose spikes and the accompanying insulin spikes appear to be the root cause of obesity and multiple other chronic diseases. Please doubt my word and research these facts for yourself. Some experts argue that *glycemic load* is more important than glycemic index, but, even if true, that doesn't make the glycemic index of a food unimportant. The great majority of my patients express disbelief the first time I tell them that eating wheat is slowly turning them into fat diabetics. Only after I repeat this several times and explain the reasoning behind it and after the patients have lost weight by stopping or slowing their wheat intake do they begin to believe and understand that the "facts" about wheat that they thought they knew were just part of another medical lie.

The truth is that everything from cataracts in the eye to arthritis in the knees, from high triglyceride levels to high blood sugar levels, are largely caused by eating multiple daily servings of foods that contain wheat. It appears that eating wheat causes these problems just as quickly as (or even quicker than) eating a jelly donut. You can easily find the few minerals and vitamins in wheat products (white bread is virtually devoid of nutrients) in other, healthier foods that have more acceptable glycemic indexes. Why do you think wheat is pushed as aggressively as it is by Big Food and by the medical experts it funds?

Big Food (the huge corporations that profit from manufacturing and marketing food products) can make anything and everything, from pizza crusts to cookies, with inexpensive wheat flour. Given all the big-government subsidies given to wheat producers, they can make it very, very cheaply, thus leading to increased profits. What a hugely profitable run Big Food has had by marketing and selling wheat as a health food. It's a shame that this wheat doesn't live up to all the hype.

The wheat contained in all the food products on store shelves today is very different from the wheat of our ancestors. Today's wheat is a semi-dwarf hybrid wheat that was starting to be bred in the 1960s, and it's become the only type of wheat in products on today's grocery shelves. It has a much higher gluten content than older varieties of wheat, such as einkorn. Many experts are increasingly finding that this hybrid wheat leads

to increases in inflammation both in patients with documented celiac disease and in normal patients who don't have this condition.

The gluten and other proteins in today's hybrid wheat seem to contribute to gut inflammation and leakiness, both of which can lead to body-wide inflammation and possibly even to autoimmune conditions such as hypothyroidism and lupus. I've had several patients tell me of enjoying increased weight loss and mental clarity, among many other benefits, after greatly decreasing wheat in their diets. Until further meaningful research explores these connections, it's best to minimize wheat in your diet, even if you do not have celiac disease. Two good general rules are to avoid any product that comes from a factory in a cardboard box and to avoid all bread, crackers, and pasta. I know some of you are feeling anguish at the very thought of eliminating these foods from your diet, almost as if you are addicted to them or something.

Speaking of addiction, research has uncovered convincing evidence that wheat contains substances that partially activate the opiate receptor in the brain (which causes activation of the pleasure centers) and have addictive potential. Several experts in the field consider substances in wheat food products to be habit-forming, which could explain why we want to eat every two to three hours when we're trying to live on a low-fat whole-grain diet. Many people find that they strongly crave these products a few days after they stop eating them. Many fail in their diet attempts and go back to eating as they did before. We need to do further study on this subject, but it's quite possible that the craving you have for baked goods is an actual addiction.

A newer drug being used to assist weight loss, called naltrexone, works by blocking the pleasure receptors in the brain. It can prevent the food cravings and thus lead to weight loss. It takes five to fourteen days to break the cravings associated with wheat after you stop eating it. After that, you can pretty much take it or leave it. I suggest that you leave it. I've had many patients tell me they felt tired and achy for two weeks after stopping grains. Many of them compare it to a time they tried to stop caffeine. However, once they pass the two-week mark, they feel better both mentally and physically, and the weight loss begins.

DO AS I DO

These days, I rarely eat any wheat at all. If pizza is the only choice available at a meal, I eat the toppings and leave the crust behind. I order meatballs and the sauce and have the server hold the noodles (which seems to upset servers for some reason). My health and weight have responded remarkably to this way of eating.

I went from being a fat-assed doctor who told my patients to lose weight to a doctor who leads by example when it comes to his waistline. Sometimes I do eat an occasional treat of something containing wheat, but I am fully aware it is just that: a treat. It isn't real food for nourishing my body.

HOMEWORK

It's apparently going to take most doctors another decade or two to catch up on their reading when it comes to wheat and its negative effects on human health. Therefore, you can help your doctor start to catch up on this important information after reading these two excellent works.

Book: *Wheat Belly: Lose the Wheat, Lose the Weight, and Find Your Path Back to Health* by William Davis, MD (2014)

Dr. Davis does an excellent job of breaking down the arguments and exposing the flawed science that has fooled modern medicine about this topic.

Book: *Grain Brain: The Surprising Truth about Wheat, Carbs, and Sugar—Your Brain's Silent Killers* by David Perlmutter, MD (2013)

Dr. Perlmutter presents overwhelming reasoning for why you should get wheat out of your life, your belly, and your brain.



Chapter 7

THE PYRAMID OF FOOD LIES



**Often the less there is
to justify a traditional
custom, the harder it is to
get rid of it.**

—Mark Twain



THE LIE

The USDA Food Pyramid and MyPlate models offer the healthiest way to make food choices. If you follow them, you will have better health.

WHY YOU SHOULD CARE

The logical conclusion is that the obesity and diabetes epidemics that our society is suffering from must be directly related to our diets. Choosing the wrong foods on a daily basis can result in you being overweight and sick, or worse. Along with not smoking, making smart food choices is the most important daily health decision you make. If the Food Pyramid and MyPlate guidelines are good for our weight and our health, then we should follow them. If the Food Pyramid and MyPlate guidelines are good only for the profit margins of Big Agriculture and Big Food, then we should look elsewhere for dietary advice.

SUPPORT FOR THE LIE

Many references to expert consensus, as well as several studies with worrisome conclusions that were based on iffy research, are used to support the Food Pyramid and MyPlate food choice guidelines. There is no meaningful research showing that people who adhere to the Food Pyramid or MyPlate models will have healthier body weights or better overall health. The federal government and every expert will, however, tell you to follow the Food Pyramid and MyPlate guidelines.

THE COMMON SENSE

For 99.99 percent of human existence on this planet, humans have been slim, fit, and diabetes-free. We never, as a species, ate the amounts of grains and low-fat dairy that are recommended by the USDA Food Pyramid and MyPlate guidelines. It stands to reason that we should eat as our ancestors did because they survived, thrived, and reproduced from the beginning of their existence to the day you were born. Of course, diets varied from region to region and from season to season, so there is not one single formula that we all must follow. Less important than what you *should* eat is what you *shouldn't* eat.

Some ancestral diets were very plant-heavy, whereas others consisted mainly of animal products. Both sets of ancestors thrived, even though their diets were very different. The few things that none of our ancestors consumed until a few hundred years ago were grains in any quantity, low-fat dairy, and high levels of sugars and processed starches. Our DNA is not yet able to use these products as sustenance for keeping our bodies healthy and lean. Obesity rates have increased steadily since the USDA introduced the Food Pyramid and MyPlate guidelines.

THE RESEARCH

If you want to understand how an agency like the USDA runs, then just Google *food pyramid history*. You will read how Big Food and Big Agriculture got the final say in these guidelines. You also will learn how these corporate giants got to make drastic changes to the Food Pyramid guidelines before those guidelines were published.

For example, Big Food and Big Agriculture companies got to proofread and change some of the guidelines after the nutrition scientists had finished with them but before the public saw them. Keep searching the Internet, and you will have as much trouble as I did finding any research that proves the Food Pyramid or MyPlate system does anything positive for your health. Good luck in your search, and don't be too disappointed with your government and Big Food. You might have done the same thing had you been in their shoes.

THE TAKE-HOME

The USDA Food Pyramid and MyPlate guidelines repeat many medical lies. This pyramid of disease encourages you to eat more starches, more dairy, less fat, fewer veggies, and less meat than you should. The amount of grains (breads, crackers, pasta, cereals, and so on) recommended is ridiculous, and the amount of low-fat dairy recommended is worrisome. As you would expect, healthy fats and salt are demonized. Low-fat and fat-free dairy is pushed as the healthiest choice, whereas healthy fats are lumped in with unhealthy fats and “vegetable” oils.

You should now be asking, “Why would my government publish this sort of thing if it wasn't correct and helpful?” That's a very good question. The answer might surprise or sicken you (or both). When the USDA was

designing the Food Pyramid, it initially recommended five servings of grains and five to nine servings of fruit daily. The Pyramid was originally designed by nutrition experts who knew a thing or two about human nutrition. However, as government is prone to do, the USDA let Big Food and Big Agriculture take a look at the suggested Food Pyramid guidelines before publication.

In the end, the government allowed profit-driven corporations to make changes that made the guidelines more acceptable from the viewpoint of the corporations, their boards of directors, and their future profits. When the proposed Food Pyramid came back from the corporations, it had been violated to protect their profits. The guidelines thereafter recommended six to eleven servings of grains (up from five) and only two to three servings of fruit (down from five to nine) daily. Dairy had gotten a section of its own, as if it were a necessary food category for all humans to consume, even though 80 percent of the people on the planet are unable to consume dairy. Also, processed and “junk” foods were lumped in with natural, whole foods in all the guideline sections. The agency that most people assume is watching over their food and their health had perpetrated an embarrassing and worrisome sellout. This is another story that you can research on your own.

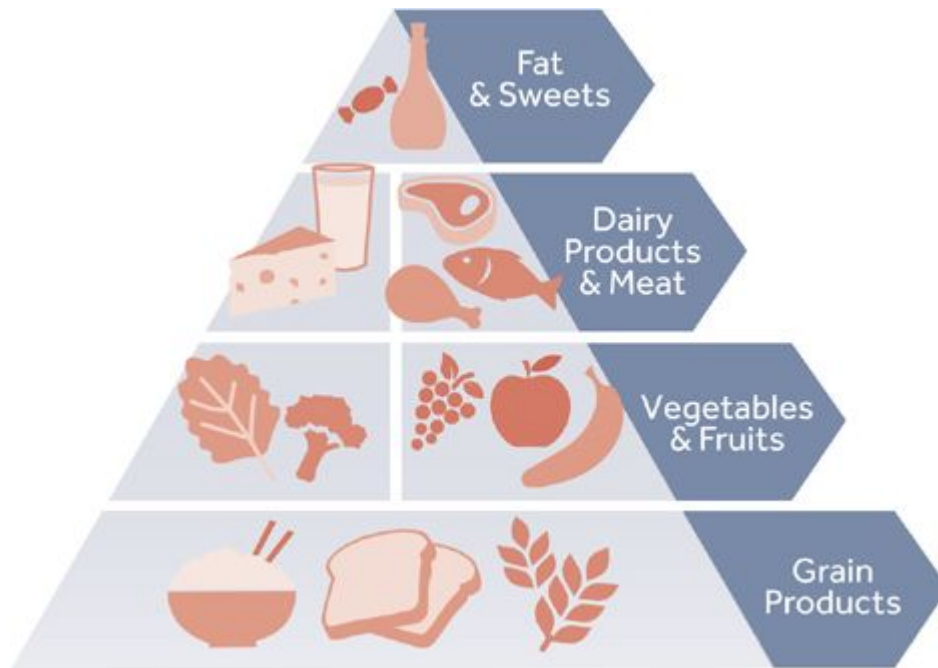
For most of our species’ existence on this planet, we have been hunter-gatherers and/or nomads. We never raised or ate grains in any meaningful amounts. The grains we grew and ate barely resembled the Big Agriculture wheat of today. Our ancestors always ate the highest-fat part of their meals first. If one of our ancestors had requested something low-fat, he would probably have been stoned to death for stupidity. As our DNA has evolved over the eons, it grew accustomed to certain foods and never had to deal with certain other things that we’re now told are “healthy” foods.

If you could go back in time and transport your forty-seventh great-grandfather to the present day, he would most certainly be muscular, lean, alert, and sharp, even in his elder years. If you made him follow the Food Pyramid guidelines (and you would have to make him; he wouldn’t do it willingly), he would become fat, sick, and sluggish in less than a year. His DNA would have no idea what to do with all the starches, sugars, and low-fat dairy. Eating those things would put fat on his belly, waist, and butt, as well as inside his liver. It makes sense (since we share the exact same DNA) that the reverse should also be true. If you were to take a modern human

(you) back in time and feed him only what his distant ancestors would have eaten, you would change him from fat, sick, and sluggish to muscular, lean, and sharp.

Because the guidelines are not mandatory for most of us, people don't give a lot of thought to the Food Pyramid and MyPlate; however, they should. Even though you might not consult the Food Pyramid and MyPlate guidelines, any institution that prepares food and receives federal funds—like public school cafeterias and most hospital cafeterias—have to follow the guidelines. Our growing children and the sickest among us are often trapped in situations where they have no choice but to eat according to the USDA's Food Pyramid and/or MyPlate guidelines. This is a danger to students and patients, and it's shameful for doctors and nutrition experts to lazily allow this to happen. These experts falsely believe that the USDA is in business to promote health, forgetting that the A in USDA stands for agriculture (Big Agriculture), not health. However, you can choose to eat properly, according to the needs of your DNA, and to try to make changes at your local school and hospital. You should start with yourself and your diet first, though.

If your doctor tells you the key to losing weight is to cut back on calories, exercise more, and follow the Food Pyramid or MyPlate guidelines, you should get up, politely walk out of the interview, and find another doctor. Any doctor who says this is revealing a complete absence of thought or effort on his part. Therefore, you probably won't be able to educate him to be your partner in health.



DO AS I DO

I would never punish my body by eating according to the Food Pyramid or MyPlate guidelines. I eat according to my DNA, as my ancestors ate. If I did anything less, it would be a betrayal to both. Of course, I occasionally have a treat that I know is not good for me; we all do that.

With my patients, I use the example of the honey tree. Probably once every year or two, our ancestors would have had the luck to find a bee-filled honey tree and the bravery to attack it. I can picture them lying around in a sleepy sugar coma for days after indulging in this special treat. Occasional indulgences like this aren't harmful, but daily treats can lead to obesity and disease.

HOMEWORK

It seems that some people, and some doctors, just can't shake the belief that *if the federal government says something, then it's the truth*. Because you have only one life and you want it to be a healthy one, I recommend you stop believing big government and read this excellent book.

Book: *Death by Food Pyramid: How Shoddy Science, Sketchy Politics and Shady Special Interests Have Ruined Our Health* by Denise Minger (2014)

Denise proves you don't have to be a doctor or researcher to write meaningfully on the topics of nutrition and health. After reading her book, you'll always translate terms such as *government guidelines* and *government recommendations* to what they really mean: *special interest groups came up with this recommendation to benefit their bottom line, not my health.*



Chapter 8

EXERCISE IS GREAT, BUT IT WON'T HELP MUCH WITH WEIGHT LOSS



**I firmly believe that if the
whole *materia medica*
could be sunk to the
bottom of the sea, it
would be all the better for
mankind and all the worse
for the fishes.**

—Oliver Wendell Holmes



THE LIE

If you exercise more, you will lose weight.

WHY YOU SHOULD CARE

Being overweight, even a little, is dangerous for your long-term health. It's vital that you know how to spend your time, effort, and money to reach and maintain a healthy weight. If exercise does lead to significant weight loss, then you should do it faithfully, even if you don't enjoy it. If, on the other hand, exercise does little to cause significant weight loss, then you should focus your time, effort, and money elsewhere and stop feeling guilty about not having joined a gym.

SUPPORT FOR THE LIE

Almost every doctor in the world will tell you this medical lie. The doctor will look at you like you're from Mars if you ask to see the research proving it. To doctors who haven't read the research about the futility of exercise with regard to weight loss and who still believe in the *all calories are equal* and *burn more calories than you eat* lies, it seems self-evident that the more you exercise, the more weight you will lose. When we look for research to back up this claim, we come away empty-handed. Expect every doctor and expert to tell you this exercise-to-lose-weight lie and to belittle you if you doubt it. You should also expect every gym, sports equipment manufacturer, and sports clothing manufacturer to tell you this same lie. It is in their financial best interest to do so.

THE COMMON SENSE

Common sense is sometimes wrong; this is why we humans came up with the scientific method; it was scientists' attempt to remove fallible human nature from the equation where important things like scientific conclusions and medical advice were concerned. In the case of this exercise-to-lose-weight lie, it seems to make perfect sense that the more you exercise, the more calories you will burn, and therefore the more weight you will lose. When you eat, you take in calories, right? When you exercise, you burn calories, right? So, if you exercise enough, you should be able to burn off any number of calories you have eaten to create a *calorie deficit*.

It seems like a simple solution. Just join a gym or buy some home exercise equipment, use it daily, and you'll be on your way to a leaner body. This is one of the times we need the scientific method to protect us from our "common sense." This line of reasoning makes so much sense to us that, even though the research shows that exercise is all but useless for weight loss, doctors still repeat this medical lie to their patients all the time.

THE RESEARCH

Research studies uniformly show that exercise is a very poor method of weight loss. More than sixty meaningful studies show very little benefit from exercise as a means of losing weight. As a young doctor, if someone had said those two sentences to me, I would have laughed at them for saying such foolish things; most doctors still would laugh. Please do some research to verify those statements for yourself. Then stop feeling guilty because you hate the treadmill, and focus your money and effort elsewhere.

THE TAKE-HOME

Although it might be hard to convince yourself of this, it has been proven, beyond a doubt, that exercising more is a terrible method for losing weight. You may need to repeat this several times while looking at yourself in the mirror before you believe it. You might need to get up, take this book into the next room, and whack your spouse over the head with it (but not too hard). Tell them to read that sentence aloud and then shut the hell up about hassling you to exercise more! This medical lie is still repeated daily for several reasons: the commonsense issue, money-making opportunities, and our seeming need to use guilt as a motivator.

Common sense is a very useful tool. It helps us figure out the world and all the problems it throws at us on a daily basis. When you drop a ball, you know which direction it will travel, and you also know what will happen when it hits the floor, even if you have never dropped that particular ball before. Common sense gives us hundreds of mental shortcuts that save us time and effort. Sometimes, however, common sense can fool or confuse us, and this medical lie about exercise is one of those times. Even now, you may be reading this with a bit of suspicion, because it seems to make so much sense that exercising more will lead to significant weight loss. Profit-hungry corporations are quick to exploit this error in common sense to

make a fortune. The companies do it in both blatant and subtle ways. They probably truly believe this lie themselves. There is money to be made on both sides of the equation. Food companies advertise to associate their unhealthy products with all kinds of sports, whereas gyms and exercise equipment companies cash in by selling you the things you need to use to burn off more calories than you eat.

Imagine that you are in the business of selling granola bars. You know they don't contain much in the way of nutrition, and they contain lots of sugar. Still, they taste so darn good that people are tempted to buy them anyway. How could you help your customers give in to temptation and buy your granola bars? What if you told them all they had to do was burn more calories by exercising more and they could enjoy all the granola bars their bellies desire without any consequences? You could even include a discount coupon in your packaging for the local gym to encourage your customers to exercise more. Your granola bars might take on the image of being health conscious.



Food and beverage companies have been doing things like this since the 1920s. Ads showed famous athletes drinking a cola after a vigorous ball game or showed children enjoying their treats after coming in from playing outdoors. Food and beverage companies don't want you to know what the research shows about the relationship (or lack thereof) between exercise and weight loss. If you knew without a doubt that no amount of exercise would erase the damage done by eating those granola bars, then you just wouldn't eat them.

Now imagine you're selling sportswear or athletic shoes. How could you take advantage of this error in thinking to make a fortune? You know that almost half of your customers are obese, so all you have to do is help them see that by exercising in your new shoes or your new line of spandex, they will be able to lose weight by burning off all calories from the food and beverages they've consumed. You could have the same athlete who drank the cola after his big game wearing your shoes *during* the game. That would tie everything together. Can you see how companies get in your wallet coming and going? First, you buy the food and beverage because you have plans to exercise more and burn off the calories. You then buy the shoes because you need them so you can run farther and faster to burn off all the calories you've consumed. Companies selling athletic equipment, shoes, clothing, and workout videos don't want you to know about the research because, if you did, you would certainly save your money rather than wasting it on their products.

Guilt can be used in many ways to exploit this error in common sense and lack of knowledge about the true nature of the research. Your doctor might imply that you're to blame for being overweight because you eat too much and don't exercise enough. By doing this, your doctor is relieved of the responsibility of not educating you correctly on how to lose weight, and he places all the blame (guilt) on you because you aren't doing the right things. Advertisers also exploit your sense of guilt. The shoe company shows dedicated models exercising in their shoes. You will look at these ads and feel the guilt in your gut because you'll think, "I'll look like that model if I exercise more." You know you need to buy those shoes and start running today. The granola bar company tries to erase the guilt you should feel from eating their worthless bars by helping you make plans to exercise more in the future to burn off the calories.

You're caught in an endless guilt cycle. You feel guilty for eating the granola bars, and you feel guilty for buying the shoes and not using them as much as you should. To make things worse, your doctor, who should know better, confirms all this guilt by pointing out that your extra weight is all your fault anyway. To add insult to injury, you have a much lighter wallet because you spent all your money on granola bars and shoes! None of this guilt helps you achieve your health goals.

Don't spend your time, effort, or money on hours of exercise for the sole purpose of losing weight, and definitely don't invest in all the shoes,

clothing, and gym memberships advertisers tell you are necessary to make exercise successful. Many people spend hours each week slaving away at a gym they hate and spending money on memberships, shoes, and other equipment to help them exercise more. When this doesn't work to help them achieve their goals, they feel guilty for their failure. They are sure that it would have worked if only they had been more dedicated.

Let me be clear about exercise and what it will do for you. It's wonderful for your mind, body, and spirit in hundreds of ways. Exercise will make you healthier and happier (if you're doing exercise you enjoy), but it will not help you lose weight. Many studies show that exercise does everything from decreasing your risk of dementia to building good-looking muscle, so there are plenty of benefits to exercise. But don't spend your time, money, and effort on exercise because you want to lose weight when you'd be better off putting your effort toward strategies that actually work.

If your doctor tells you the key to losing weight is to cut back on calories and to exercise more, politely walk out of the interview and find another doctor. Or you could maybe hand the doctor a copy of this book and tell him he's perpetuating a careless and damaging lie when he tells an overweight patient to exercise more.

DO AS I DO

I'm very active and exercise a lot, but I never, ever "work out." I jump on the trampoline with my kids, cut down trees, lift heavy things on my little farm, and sometimes run really fast. However, I never do any of these things for the purpose of losing weight. I wouldn't join the gym if it were free, and you couldn't pay me to run on a treadmill.

Do what you enjoy. Don't work out; go outside and play! Fun, playful exercise is great for your body, mind, and soul, but you need to look elsewhere for meaningful weight loss. If you truly enjoy running on a treadmill, then, by all means, do it daily. But, don't expect that activity to lead to permanent weight loss.

HOMEWORK

You probably won't get much help from your doctor on this subject. You're better to read the following book and then let your doctor borrow it. He

might thank you for helping him to stop mindlessly repeating this medical lie.

Book: *The Calorie Myth: How to Eat More, Exercise Less, Lose Weight, and Live Better* by Jonathan Bailor (2015)

This is one of the very best books I have read that explains how food quality, not food and exercise quantity, is the key to meaningful weight loss.





Chapter 9

NUTS AND SEEDS DON'T CAUSE THIS PROBLEM



**The specialist is too commonly
hypertrophied in one direction and
atrophied in all the rest.**

—Martin H. Fisher



THE LIE

Eating popcorn, nuts, and seeds will either cause diverticulitis or cause your diverticulitis to flare up.

WHY YOU SHOULD CARE

Diverticulosis is a condition that occurs when small pouches form and push outward through apparent weak spots in the wall of the large intestine. The pouches often develop in the lower part of the large intestine. They are common in individuals who eat a Western diet and are older than forty. Most people with diverticulosis do not have symptoms or problems. However, some people have attacks of diverticulitis (inflammation or infection in those small pouches) that can be quite severe. If eating nuts and seeds causes flare-ups of diverticulitis, then you should avoid eating those foods. However, nuts and seeds are very nutritious. Therefore, if it's a medical lie that nuts and seeds cause flare-ups, then everyone with diverticulosis should enjoy them for their taste and many health benefits.

SUPPORT FOR THE LIE

There is no scientific support for this medical lie. I couldn't find one large, reputable study that supports this statement. *None*. As I reflect on this, it makes me worry about doctors who repeat lies like this with no supporting research because the lie appeals to our common sense.

THE COMMON SENSE

Common sense is once again behind how people—even doctors—widely believe and repeat this medical lie. It seems to make good common sense that if you have small pouches in the lining of your large intestine, then eating tiny things like seeds might increase the risk of diverticulitis. It also makes sense that one of these little seeds could clog the opening of one of the pouches and cause problems because clogging the opening could cause the pouch to become inflamed or infected (which is the definition of diverticulitis).

THE RESEARCH

One very large, well-done research study shot this medical lie in the head years ago. It was published in *JAMA (Journal of the American Medical Association)*, and it should have been required reading for every doctor in the country. However, doctors and news sources refuse to let this lie die the death it deserves. This study included thousands of participants, and it showed, without doubt, that some foods do increase your risk of getting diverticulitis. However, seeds, nuts, and popcorn are not on the list of problem foods. The patients in the study who reported eating the most nuts, seeds, and popcorn were the least likely to get diverticulitis. Yes, you read that right.

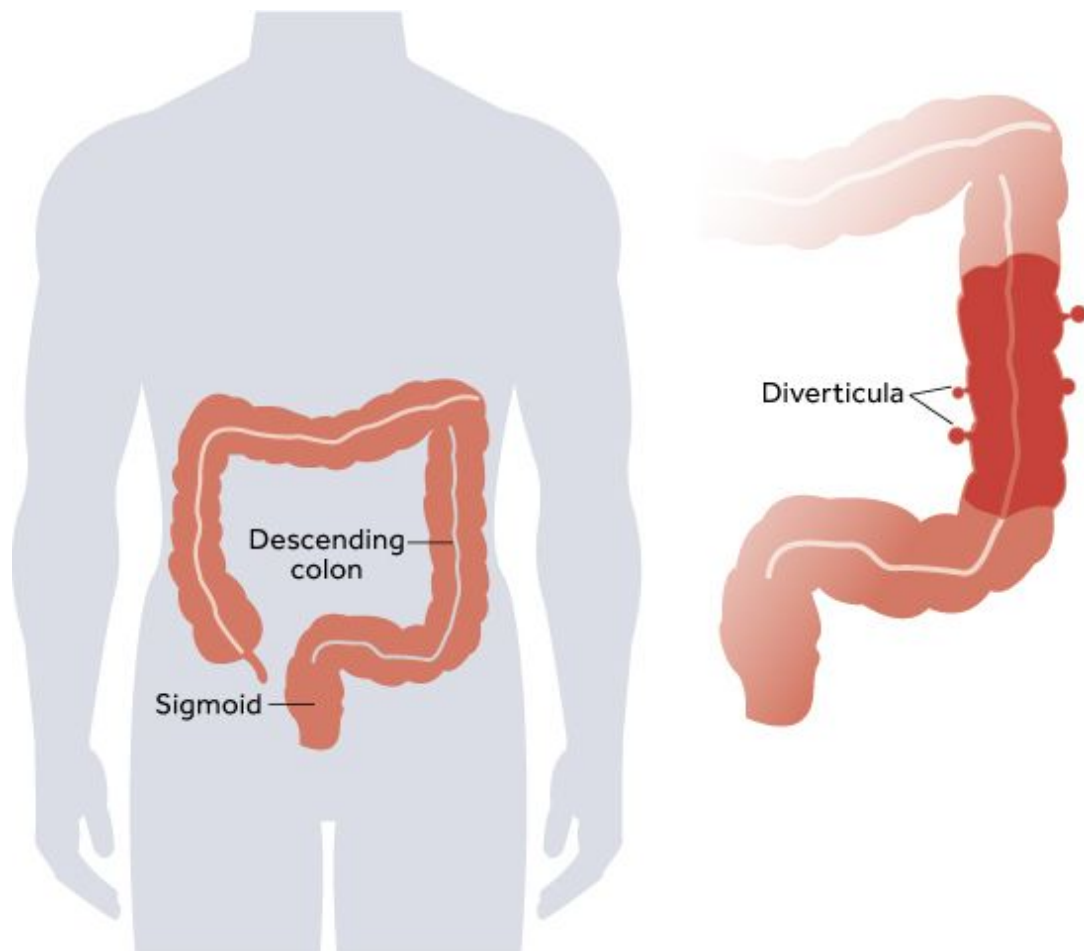
This lie is very revealing in that it demonstrates that doctors don't need any medical research to believe fervently in a medical lie and to repeat it to their patients. Very good doctors thoughtlessly repeat this lie to patients who would really benefit from the nutrition in nuts and seeds. If doctors would become familiar with the study in *JAMA*, they'd know that the nuts and seeds probably protect patients from having bouts of diverticulitis.

THE TAKE-HOME

Nuts and seeds are some of the healthiest foods you can eat. The nutrients and fiber they contain are great for your health. When I was in my residency training and first taught the lie that nuts and seeds are a problem, I was suspicious, but, as is typical of a resident, I was so tired and busy I had no time to research the information. This lie was reinforced many times in my training by experts in the field. It was only after I completed residency and started my practice that I had time to look into the research behind this lie. As is often the case in medical practice, a patient must suffer for a doctor to learn.



I had sent a patient who was having severe bouts of diverticulitis to see a gastroenterologist (a specialist in the stomach and intestines) in a nearby metropolitan medical center. The patient went to see the specialist and returned to see me a few weeks later. When I walked into the exam room, my patient was anxious about telling me what he had learned because he feared I would be offended. He knew I encouraged all my patients to eat a natural whole food diet, and what the gastroenterologist had told him contradicted my advice. With a little prodding, I learned that this respected specialist had told the patient to stop eating nuts, seeds, and popcorn because they were probably getting trapped in his diverticula and causing his bouts of diverticulitis. I immediately remembered that I had been suspicious of this theory while in residency, but I didn't argue with my patient. I just told him to give it a try and see how it went. Meanwhile, I made myself a mental note to research as soon as possible.



It didn't take me long to find the study I mentioned earlier. There was just one problem. The study had been published in 2008. But even in 2012, the specialist had told my patient to avoid nuts and seeds. I kept rereading the study, thinking that I must be missing something. However, the study showed very clearly that nuts and seeds do not cause flare-ups of diverticulitis. The specialist I had sent my patient to was one of the best in our part of the country. He was very well respected, yet he had told my patient a medical lie—a lie that would not help the patient and actually might harm him. This was *the lie* that made me seriously wonder if there were other lies out there, including lies I had been telling my patients. Did this specialist, whom I greatly respected, not read the medical journals? Did he not research the things he told patients before he shared the information?

I saw this patient again about a month later because he'd had another severe bout of diverticulitis. (I had resisted the urge to call him sooner to tell him of my discovery.) After treating my patient, I gave him a copy of the *JAMA* article. I explained, as respectfully as I could, that the specialist was probably wrong to recommend not eating nuts and seeds. My patient agreed, saying he had avoided all three completely but still had another flare-up. He wanted to know what I thought was causing these flare-ups. I explained what I had read in the article, which said that bouts of diverticulitis were associated with smoking, being overweight, eating red meat, and taking NSAIDs (anti-inflammatory medicines like ibuprofen and naproxen).

My patient was obese, he smoked, and he took ibuprofen almost every day. Armed with this real medical information, he was able to start eating nuts and seeds again (which actually protected him from bouts of diverticulitis), and he was able to refocus his attention on the true causes of his suffering. The specialist hadn't mentioned the patient's weight, smoking habit, or ibuprofen use at all during their visit. The doctor had ordered and performed a colonoscopy (in which a long scope is inserted into the large intestine) and then told the patient to avoid nuts, seeds, and popcorn. That was all he did for my patient.

At first, my patient was skeptical of what I said because I was only his family doctor rather than a specialist. However, he took a copy of the study (I had printed copies to give to patients with diverticulosis) and said he would read it and consider what it had to say. My patient, being a smart man, did just what he promised to do. He returned a few weeks later for my advice on how best to lose some weight and quit smoking. During his visit, he told

me that while researching diverticulosis he had discovered hundreds of Internet news articles and blog posts proclaiming the results of the study I had given him. He wanted to know how it was possible that the respected specialist had given him such terrible advice.

I made some excuse for the specialist (doctors are notorious for protecting their own, despite the disastrous consequences of another doctor's ignorance) and steered the conversation back to the patient's diverticulosis. We discussed ways he could control his joint pain aside from taking ibuprofen all the time. Over the next few months, he quit smoking, lost a few pounds, and stopped taking the ibuprofen in favor of getting weekly massage therapy. Now he very rarely (less than once a year) has a flare-up of diverticulitis, even though he eats nuts and seeds every day.

We can, therefore, add diverticulitis to the growing list of things caused by being overweight, smoking, and taking too many pills. We seem to be uncovering a pattern that these three things are dangerous to our long-term health. They won't kill you today, but they will harm you a little each day until the damage builds to the point that it causes a health catastrophe in the future.

You can do an Internet search for diverticulitis and seeds to find hundreds of bloggers and news outlets who know nuts and seeds don't *cause* diverticulitis. Therefore, if your doctor tells you this medical lie, I suggest that you get up and walk out of his office before he finishes his next sentence. He is either unread, lazy, or both, and you can do better for your health. You also could print a copy of the study and mail it to him, or drop off a copy of this book at his office. Maybe he will read it and give better advice to his other patients.

DO AS I DO

I love nuts and seeds and eat some every day. I don't smoke, and I try hard to keep my weight under control. I've never suffered from diverticulitis, but if I ever do, I would still eat nuts and seeds, and you should, too.

HOMEWORK

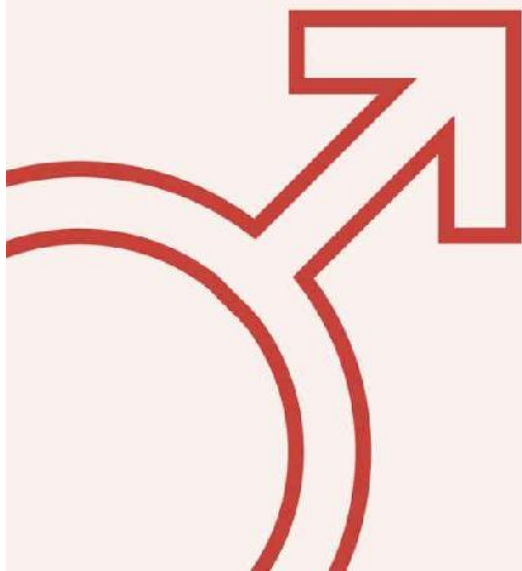
You can find the JAMA article I mentioned at <http://bit.ly/JamaDivertic>. You can read it yourself and print a copy for your doctor. After you read this article, you're going to be at a loss as to why doctors repeat this lie. Please

be gentle when you give a copy to your doctor; evidently he can't help perpetuating the myth.



Chapter 10

WILL THIS GIVE MEN PROSTATE CANCER?



**Formerly, when religion
was strong and science
weak, men mistook magic
for medicine;
now, when science is
strong and religion weak,
men mistake medicine
for magic.**

—Thomas Szasz

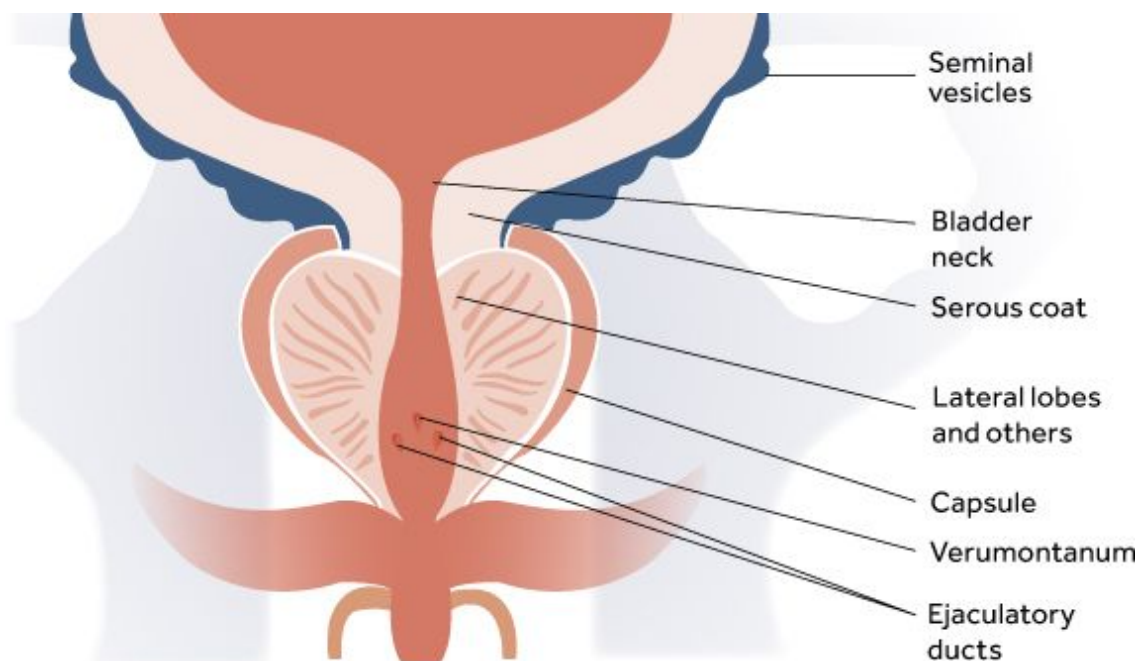


THE LIE

Giving testosterone to men causes prostate cancer.

WHY YOU SHOULD CARE

As a man ages, his testosterone level drops, which leads to a long list of negative symptoms and suffering. The symptoms can be treated easily with testosterone optimization therapy, which greatly improves a man's quality of life. So if this is a medical lie, we shouldn't be afraid to optimize a man's testosterone. However, if testosterone optimization might cause prostate cancer, then a man shouldn't take the chance of using the therapy.



SUPPORT FOR THE LIE

You'll be surprised when you hear the story of where this lie started and how little meaningful research supports it. It basically comes from one man's opinion, and that opinion wasn't based on any real research. Many other doctors and experts believed the unproven opinion of this one man and have repeated this medical lie for decades.

In the 1940s, Charles B. Huggins, MD, was working with dogs and studying their prostates at the University of Chicago. Dogs and humans are

the only animals that have trouble with their prostates becoming enlarged as they age. (Perhaps related to processed food diets? But I digress.) Huggins found that when he castrated the dogs, their prostates shrank. While looking at microscope slides of the dogs' prostates, Huggins noticed areas that looked the same as prostate cancer in humans. When he observed these areas on the slide, he noticed that they were smaller after the dogs had been castrated.

Based on what he had observed in his studies of dogs' prostates, Dr. Huggins did some limited research on humans who had prostate cancer using a lab test that no doctor would use today (acid phosphatase). He concluded that giving a man who has a prostate any testosterone replacement is like throwing gasoline on a fire; the testosterone will increase the risk of developing prostate cancer. He published an article in the very first issue of the journal *Cancer Research* to detail his results. However, he had studied only three men who had received testosterone injections. Furthermore, his report addressed only two of the men, and one of those men had already been castrated. So this medical lie about the connection between testosterone and prostate cancer is based on the results of *one* patient who had already been hormonally manipulated!

Dr. Huggins, although an intelligent expert in his field who was affiliated with a prestigious institution, had based his conclusion on almost no evidence at all. Despite the lack of substantial research to support the theory, a doctor couldn't argue against this medical lie for decades without that doctor being shunned or persecuted by other doctors. Although support for this lie is slowly dying, unthinking or lazy doctors (including urologists) still repeat it.

THE COMMON SENSE

We all start with a testosterone level of zero in the womb, and it goes up from there. We rarely check testosterone levels in healthy children or adults. If, however, a man over forty starts to exhibit symptoms of fatigue, muscle loss, or loss of interest in life, then we check his testosterone levels as part of a complete workup. Male testosterone levels peak between the ages of seventeen and twenty, and then they start to slowly decline. At some point a man's testosterone level gets so low he begins having classic symptoms, such as reduced bone mass, anemia, insomnia, reduced muscle mass, and severe fatigue. When a man's testosterone level gets low enough, he will

benefit greatly from having it corrected. Testosterone optimization has been practiced for decades in Europe and California without any increased rate of prostate cancer, but patients have benefited from a definite increase in strength, stamina, and health.

To blindly say that increasing testosterone in a man will increase his risk of prostate cancer is silly. If high testosterone levels were a risk factor for prostate cancer, then male high school seniors would be dying routinely from prostate cancer because their testosterone levels are very high. Think back to your senior year in high school, how many of your classmates had prostate cancer? That's right: not one. But, at that age, a man's testosterone levels are the highest they'll ever be. It's only as a man gets older and his testosterone level drops, or perhaps his testosterone/estrogen ratio drops, that he is at risk for prostate cancer. Prostate cancer is a disease of older men with low testosterone levels. Young men, who have high testosterone levels, never get prostate cancer. Just think about that for a moment. This commonsense fact alone should raise serious doubt about this lie in the average doctor's mind if he is thinking at all.



THE RESEARCH

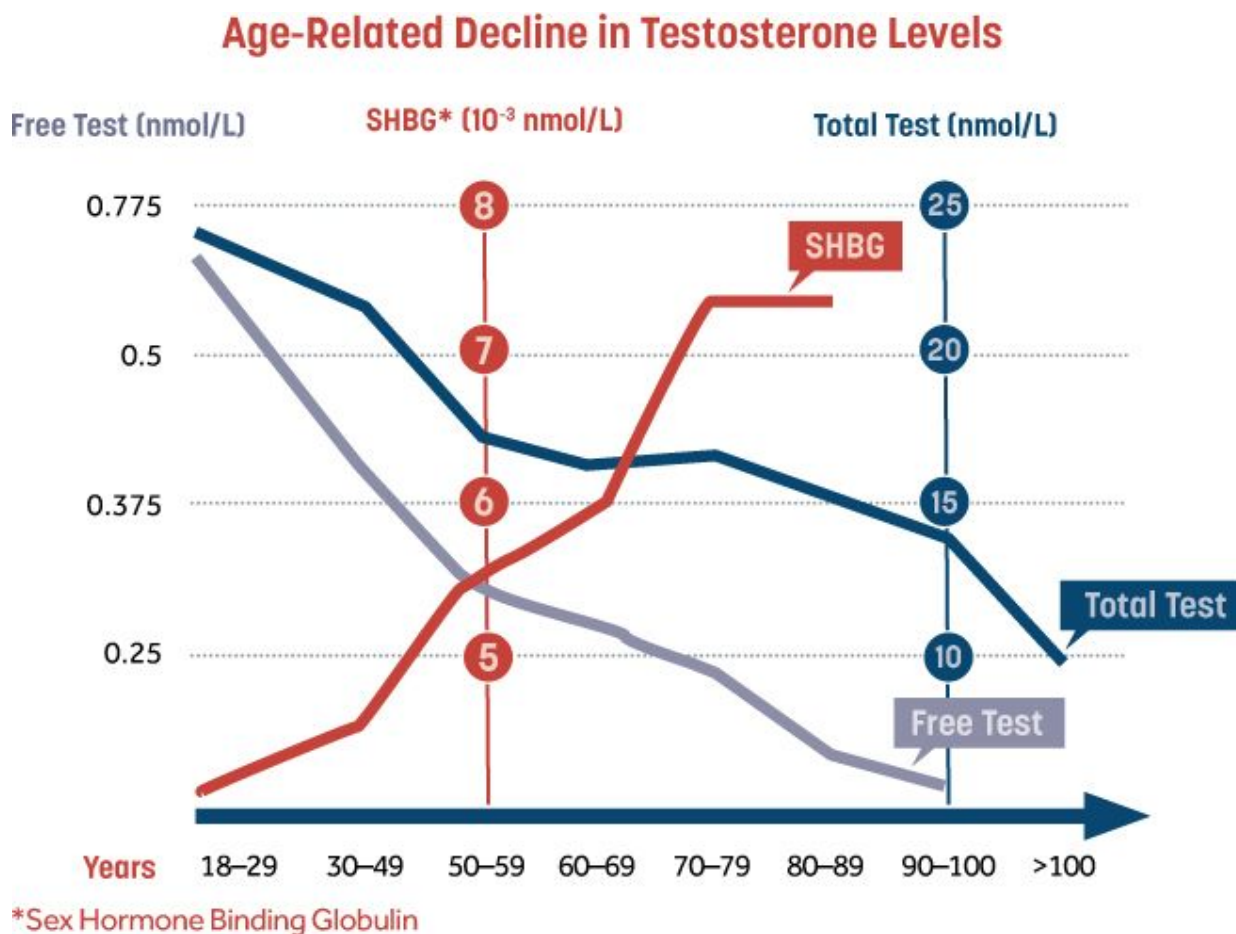
So, this lie, which has fooled many doctors and caused suffering in many patients, began with research documenting the findings of testosterone therapy on *one* patient. Since then, much research has been done in this area, and virtually all the large, well-done studies show there is no link between optimizing testosterone levels and an increasing risk of prostate cancer.

Each new, properly conducted research study is slowly but surely disproving this medical lie. Researchers are still a little skittish about their

research proposals and study conclusions because of past animosity toward this subject, but the tide is inevitably turning to show that testosterone replacement is very good at best and neutral at worst where the incidence of prostate cancer in treated men is concerned. Much more research needs to be done on this topic to find out just how beneficial testosterone optimization is for men.

THE TAKE-HOME

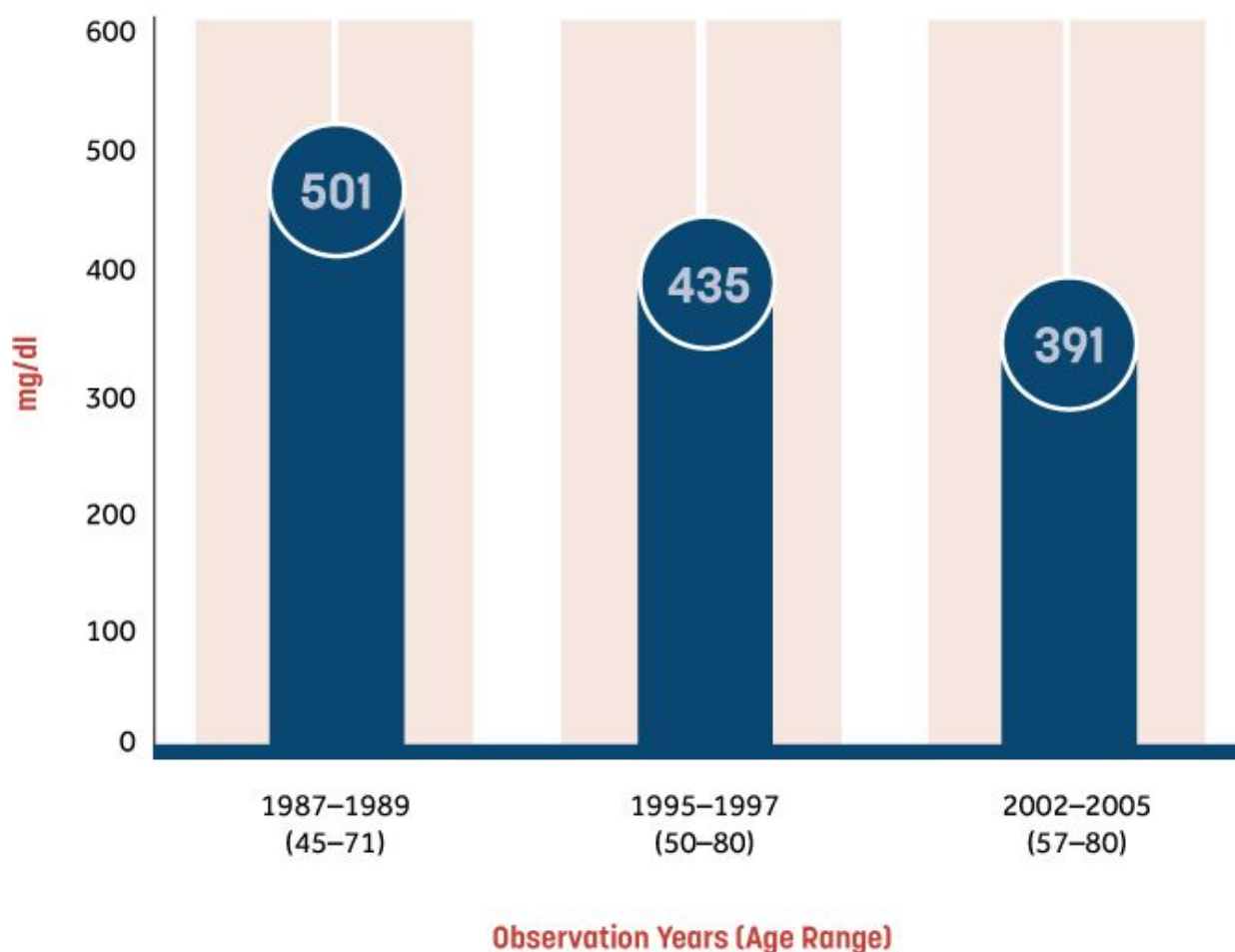
A man feels his best when his testosterone level is in the upper limit of normal. As long as a man's testosterone levels are kept in the upper range of normal, there's no evidence that there are negative risks involved.



Many years ago, the average older man's testosterone level was substantially higher than the average older man's level is today. As of now, we're not sure if this was because men previously had better diets, they were more active, or they were exposed to fewer toxic chemicals (or even some

other reason). Regardless of the reason today's level is lower than in the past, we need to fix it. I routinely find men in their thirties who have testosterone levels less than 300. (The normal range is 350 to 1,200.) This trend is very concerning because it means that these men, if left untreated, will suffer a slow, painful decline for decades. Doctors need to be optimizing their male patients' testosterone while they search for the environmental and dietary causes of the plummeting average testosterone levels.

Total Testosterone Concentrations in Men in Massachusetts Male Aging Study



Median Total Testosterone

This medical lie is a cautionary tale to all doctors and experts that they should never blindly accept what the prominent leaders in medicine say as absolute truth. Furthermore, patients should never blindly believe what their doctor tells them. Thousands of men have suffered for years and died early, unnecessary deaths because doctors were afraid to check and/or treat their patients' testosterone levels. Men deserve this level of care from their doctor, but they might find they must educate themselves on the subject so they can educate their doctor.

Medical opinion on this subject is currently doing a very slow about-face—at least among doctors who read and think. Experts are now studying the possibility that low testosterone is a cause of prostate cancer, and it seems that keeping a man's testosterone level optimized might protect him from the risk of prostate cancer in addition to preventing many of the other problems of aging. More meaningful research is necessary to clarify this area of medicine, but the current attitude among more progressive doctors is that testosterone optimization is safe, and it's most likely protective against multiple diseases and conditions. If your doctor tells you testosterone optimization is dangerous for you and will increase your risk of prostate cancer, then you have the obvious choice of finding a new doctor, or, if you like your doctor, trying to educate him.

DO AS I DO

I can keep my testosterone levels in the middle to upper range of normal with diet and activity and by avoiding as many toxins as I can. I never eat or drink anything hot from a plastic or Styrofoam container, and I also limit how many canned products I eat. The reason I'm cautious about these situations is because the components in the plastic containers and the can's lining, which contain BPA and/or BPS, are harmful. Many researchers on the subject believe the chemicals in these containers can seep into our food and contribute to lower testosterone levels, along with other problems. The minute I can't maintain a decent testosterone level with diet, exercise, and lifestyle choices, I will work with my doctor to optimize my testosterone level with a bioidentical testosterone replacement.

HOMEWORK

More and more good books and websites are addressing how men can optimize their testosterone levels. I've listed the ones I find most helpful for dispelling myths and giving good, useful information. The more you read, the less afraid you'll be about keeping your testosterone levels in the upper range of normal.

Book: *Testosterone for Life* by Abraham Morgentaler, MD (2008)

This Harvard professor tells it like it is. After reading this book, you'll have no fear of optimizing your testosterone level.

Book: *The Life Plan* by Jeffry S. Life, MD (2012)

Dr. Life offers great detail about testosterone optimization and other topics older men need to know. He teaches by leading and by setting a great example for other men to follow.

Book: *Estrogenation: How Estrogenetics Are Making You Fat, Sick, and Infertile* by Anthony Jay, PhD (2017)

If you think BPA is the only thing that should worry you about plastics, then this book will really wake you up. Dr. Jay explores all the ways plastics can degrade your health.



Chapter 11

THERE IS MORE TO WOMEN THAN ESTROGEN



**Doctors are men who
prescribe medicines of
which they know little,
to cure diseases of which
they know less,
in human beings of which
they know nothing.**

—Voltaire



THE LIE

Menopausal women usually don't need progesterone, and they definitely don't need testosterone. If they need anything at all, they need only synthetic estrogen to control hot flushes.

WHY YOU SHOULD CARE

Your hormones, more than anything else in your body, make you who you are. If your hormones are optimal, then so are you. If your hormones are lacking, then so are you. An informed doctor can diagnose and treat low hormone levels with ease. You deserve to feel your best. If optimizing all three female hormones is safe and leads to more enjoyment in life, then a woman should do it. If all that women need to be their best is fake estrogen, then we shouldn't worry about testosterone and progesterone.

SUPPORT FOR THE LIE

Women have unwittingly drawn the short straw as patients for hundreds of years. For example, *hysteria* and *hysterectomy* have the same root, which is from the Greek word for womb (*hustera*). In the past, doctors thought that when a woman acted too hysterical (outside the social norms of the time), it was because the uterus was wandering through her body and making her crazy. The solution was for her to have a hysterectomy (surgical removal of the uterus). No, I'm not kidding. That was the standard of care for medical diagnosis and treatment for many years. The smartest doctors and experts in the country at that time agreed on this diagnosis and treatment plan for thousands of women. (Keep this story in mind when your doctor tells you a medical lie and then says that all the experts say the same thing.)

Therefore, don't be too surprised to hear doctors say silly things such as, "Menopausal women never need any hormone other than estrogen." And by estrogen, they mean synthetic (fake) estrogen. Doctors might also say, "Women don't need testosterone because they don't make it naturally." I've heard licensed, practicing doctors say both of these things. Saying such a thing out loud is embarrassingly ignorant, and treating patients in this manner borders on malpractice. Healthy premenopausal women *do* make testosterone naturally. Suffice it to say there is little or no meaningful research on either side of this question, as unfair as that is. Historically, doctors and Big Pharma haven't cared enough about menopausal females'

comfort and health to thoroughly study this issue except in instances when the goal was to get a new billion-dollar baby (drug) approved by the FDA.

Let me give you an idea of the poor treatment women have gotten from modern medicine when it comes to their hormones by telling you the story of taking testosterone pills. There used to be a testosterone pill on the market for men that would increase their testosterone levels. It was called methyltestosterone, and it was marketed under several brand names. Although the pill was considered safe initially, it was later determined that taking methylated testosterone by mouth could be toxic for men's livers. The pill was no longer prescribed to men. However, this same methylated testosterone is still readily available for women as part of a combination pill that includes fake estrogen (Estratest)!

Yes, that's right. Either women's livers are magically tougher than men's, or somehow their livers just don't matter as much. Either way, I don't prescribe oral testosterone to either my male or female patients because I believe that, based on the research, it's bad for the liver, no matter who you are. If you're a woman and your doctor has been prescribing this oral testosterone, ask him how it's safe for your liver but not for your husband's or brother's liver. You should also ask him on what research he's basing his decision.

THE COMMON SENSE

According to the feedback from my patients, when women are in their late teens and early twenties, they typically feel the best they will ever feel. Their bodies look and behave how they want them to, and their mood is much more predictable and stable. For women in this age group, the rate of breast and other cancers are extremely low (almost zero). However, if we believe the average doctor's current thinking, women in this age group should have high occurrences of breast cancer and uterine cancer because their hormones are so high.

The doctor uses this same *logic* when he tells a patient who wants to optimize her hormone levels in her forties and later that it will increase her risk of cancer. If it doesn't make sense that high hormone levels increase a woman's cancer risk when she's in her twenties, then it doesn't make sense when she's in her sixties or seventies as long as she uses bioidentical hormones. Big Pharma has produced synthetic estrogens (Premarin, Prempro, and estradiol), and even though they have been proven to increase

a woman's risk of cancer, many doctors are still comfortable prescribing them, at least for a few years. However, this same doctor will most likely be very uncomfortable prescribing bioidentical hormones, which should be safe. I recommend that a woman use only bioidentical hormones to optimize her hormone levels.

THE RESEARCH

There is very little meaningful research on women's hormone needs during and after menopause. Researchers did just enough research to show the synthetic estrogens in products like Premarin were sufficiently safe for the FDA to approve the pills. After that, all meaningful research stopped. There are many studies (sponsored by Big Pharma) that demonstrate that one fake estrogen is better than another. However, no studies have been done to compare synthetic estrogens to bioidentical estrogens, although this research should be at the top of the to-do list for doctors in this field.

When it comes to progesterone and testosterone, the story really gets embarrassing. Even now, most doctors tell their patients that progesterone acts only on a woman's uterus; if she doesn't have a uterus, they say she doesn't need progesterone. Apparently we're to assume that the progesterone receptors in a woman's brain were put there to serve no purpose. Doctors view testosterone in much the same way. Most doctors have no idea that a woman needs testosterone to feel, act, and look her best. These doctors will tell you it's unnatural and dangerous to give women testosterone, even though women have testosterone receptors on their hearts and in their brains. Research is severely lacking in this area of hormone optimization, and it should be an embarrassment to doctors who claim expertise in the field of women's health.



THE TAKE-HOME

There are multiple hormones in the human body, and each one has important effects on multiple organs and systems. It's shameful for a doctor to pretend that all an aging woman needs is either to take a pill for depression or to supplement with a synthetic estrogen to get through a few years of the misery of menopause. In my opinion, it is well within the scope of practice of a good primary care doctor to optimize the hormones of his female patients and help them feel great, stay slimmer, and really enjoy life. Estrogen is certainly very important in this process, but so are testosterone and progesterone.

For a woman to feel her best, she needs to optimize all three hormones. Testosterone is just as important for heart health, energy level, and sense of well-being in a woman as it is in a man. She also needs optimized testosterone levels for good muscle tone, hair, and skin. A woman needs less than one-tenth of the amount of testosterone that a man needs, but without even that small amount, she feels physically exhausted, mentally foggy, and older than her age. Without optimized progesterone levels, anxiety, insomnia, and weight-gain become a menopausal woman's constant companions. Simple lab work before hormone optimization, and regular lab rechecks during therapy, can determine a woman's estrogen, testosterone, and progesterone levels, which makes it possible to keep the levels in the ideal ranges. Optimizing a woman's hormone levels won't change who she is, but it will make her feel like herself again.

If you're a woman who's older than thirty-five, and fatigue, anxiety, insomnia, and/or depression seem to always be plaguing you, ask your doctor to check your hormone levels when he's checking all the other labs that he checks. Ask him which hormones he will check; if he doesn't include testosterone and progesterone, ask him why. If he tells you that a woman doesn't need testosterone—or worse, if he says that it's a male hormone—let the eye-rolling and walking-out begin. (You can also give that doctor a copy of this book as a gift and inscribe it with a strongly worded message.) You deserve to feel your best, and that can happen only if *all* your hormones are optimized. Don't let your doctor's laziness or lack of critical thought keep you from being your best.

DO AS I DO

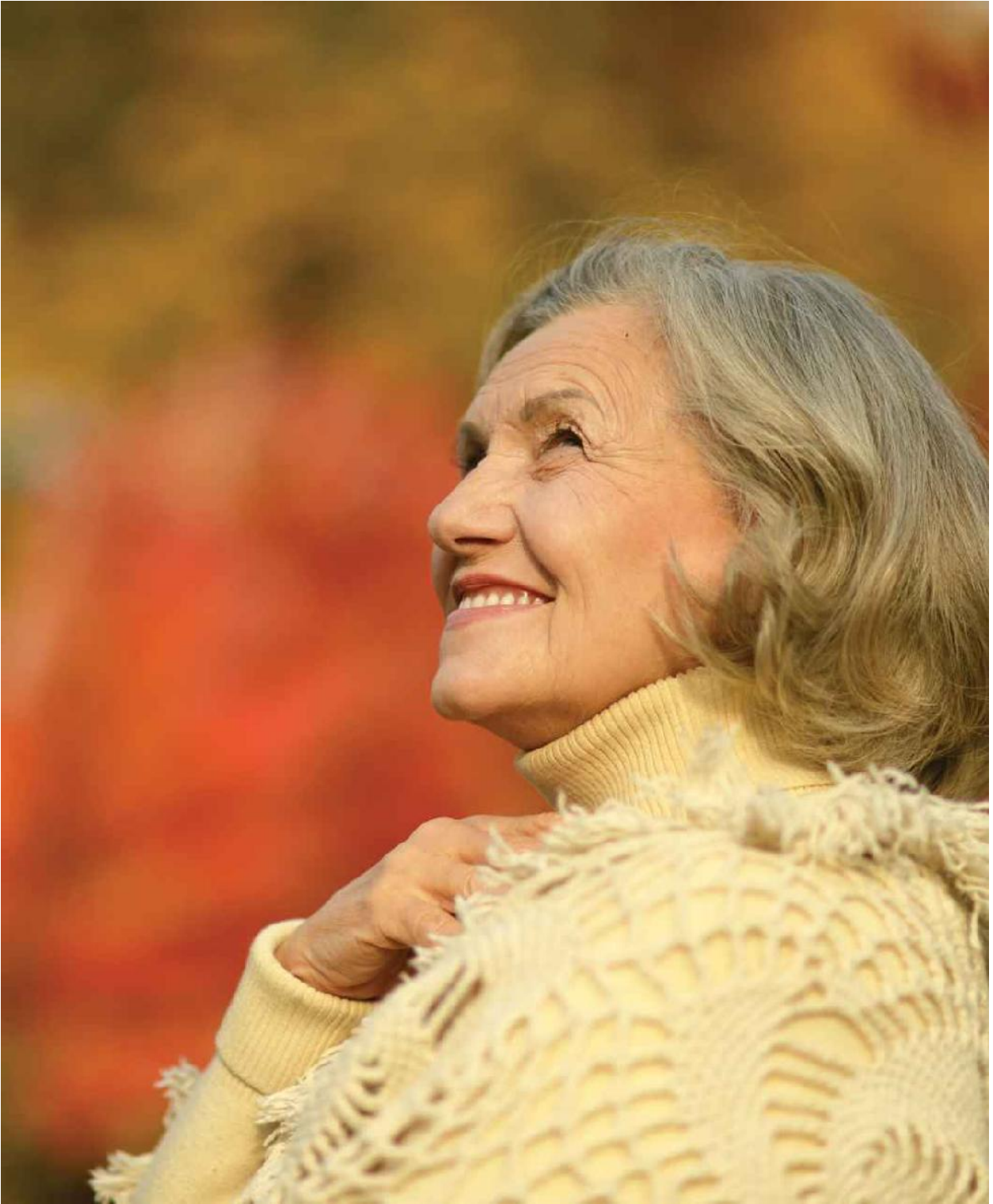
My wife has her hormone levels checked yearly, and her doctor will begin optimizing her hormones just as soon as her diet and lifestyle no longer keep them in the upper limits of normal. I would be negligent as a husband who is also a doctor if I let her suffer unnecessarily because of falling hormone levels.

HOMEWORK

The mere mention of the fact that women need something other than estrogen as they get older can switch many doctors' minds to the *off* position. Before you go to your next doctor visit, arm yourself with knowledge that will help you open your doctor's eyes or reveal that you need a new doctor. The book I'm suggesting will give you all the knowledge you need to begin your journey back to optimal hormone health. The author is a doctor who's a real advocate of women's health and a leading authority on the real hormone needs of women.

Book: *The Secret Female Hormone: How Testosterone Replacement Can Change Your Life* by Kathy C. Maupin, MD (2015)

Dr. Maupin has been an expert in gynecology for decades, and she gives women empowering information about everything their bodies need to be optimal.



Chapter 12

VIRUSES LAUGH AT ANTIBIOTICS



**Drugs are of price value
when needed, but they
are at best emergency
measures of most
temporary utility ...
The more effective they
are in the right place,
the more harmful in the
wrong one.**

—Woods Hutchinson



THE LIE

Your runny nose, earache, or cough won't get better unless you take a course of antibiotics. If you take an antibiotic, you will get over your runny nose, earache, or cough more quickly.

WHY YOU SHOULD CARE

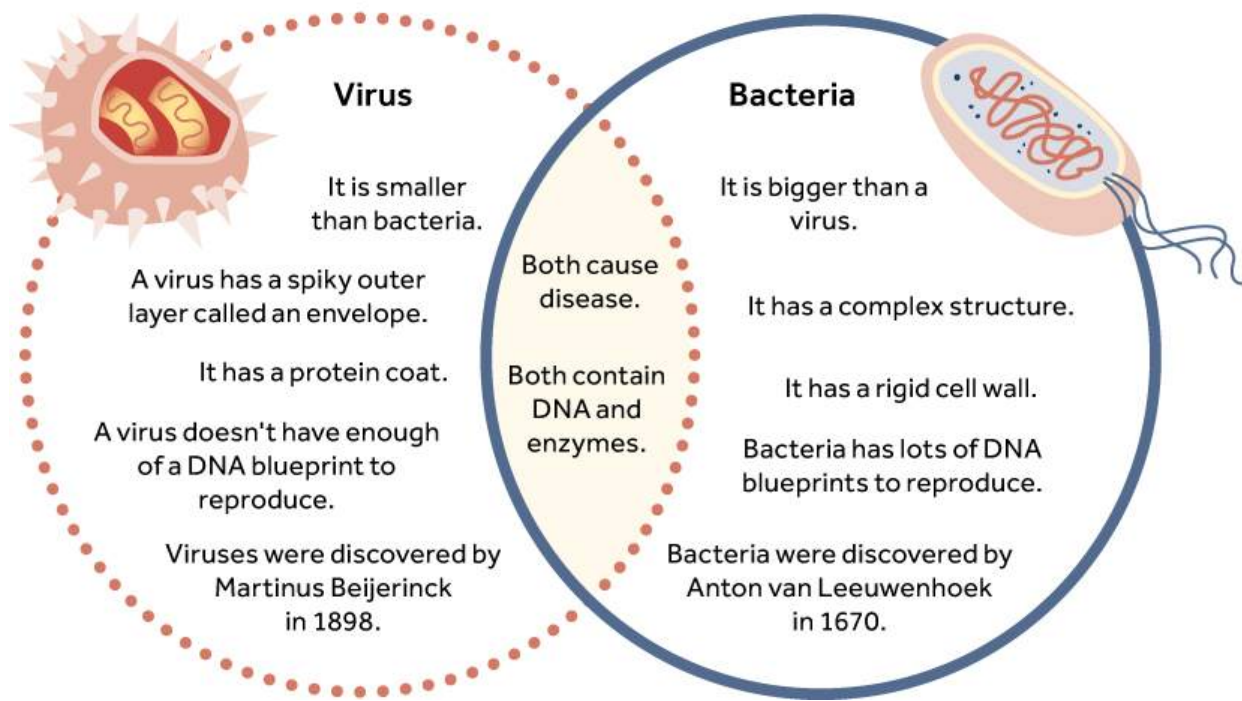
Even though we have been trained to think that taking antibiotics is no big deal, in truth it's a very big deal to take a course of antibiotics. The antibiotic can be dangerous to you while you take it, and it also can cause long-term issues with your health. If there are certain types of infections that don't respond to antibiotics, then we shouldn't take the risk of using antibiotics for those infections. For infections that do respond to antibiotics, we should weigh the risks and benefits of taking antibiotics to address them. When we take antibiotics, we always should consider additional steps to minimize other complications of taking the antibiotics.

SUPPORT FOR THE LIE

Since penicillin became known for its lifesaving bacteria-killing properties, humankind has rushed to receive this seemingly miraculous class of medicines. There is no doubt that antibiotics have saved many lives. It's also true that many a life has been taken, or made miserable, by inappropriate antibiotic use. Extensive research shows that antibiotics are effective against certain bacteria, and the research demonstrates the benefits of taking the drugs. Unfortunately, both laziness and the quest for money have led to the gross overuse of antibiotics for infections that aren't responsive to antibiotics or that would have resolved on their own without medicine of any kind. Of course, antibiotics work well under the right circumstances; there's no question about that. The question is why your doctor prescribes them so often when you don't need them and they're not helpful.

For decades, doctors have been telling this medical lie in deed if not in words. Even if your doctor has pamphlets in the waiting room about how colds and other infections are caused by viruses that don't respond to antibiotics, you might still leave his office with a prescription for antibiotics. It's almost as if doctors have been trained by demanding patients to prescribe antibiotics even when they aren't needed.

Compare and Contrast



THE COMMON SENSE

Taking any medicine when you don't need it is foolish and possibly dangerous. Medicines, including antibiotics, are powerful and potentially life-threatening tools; you should use them only in the proper amounts and in the proper circumstances. We've all learned since childhood that germs and bacteria are bad, and we should destroy as many of them as we can. We use all kinds of antibacterial products to destroy any bacteria that we come in contact with. Every homemaker's dream of a perfectly clean counter includes a bacterial count of zero.

It turns out the dream of a bacteria-free life is a recent phenomenon. Companies that are trying to sell products for profit are the primary proponents of the concept. We have lived with bacteria, viruses, and fungi—both on us and in us—since the beginning of time. It's true that some of these things are very bad for us, but the vast majority of them range from neutral to beneficial. In your body, bacterial DNA outnumber your DNA by one hundred to one. Bacteria, like people, can be friends, foes, or neutral entities. The job of doctors is to decide which type of bacteria you have and to use antibiotics only against the dangerous foes.

THE RESEARCH

Research on the effects of bacteria on the human body takes several directions. I can roughly summarize it with the following statements.

- Bacteria do not cause most infections.
- Antibiotics do not work at all on viral infections.
- Viral infections last for a few days (three to fourteen) and then go away.
- Some bacteria can make us very sick or even kill us.
- Some bacteria are beneficial to us.
- Antibiotics kill many bacteria, both bad and good.
- Antibiotics can't kill some bacteria.
- Overuse of antibiotics can lead to resistant bacteria.
- Killing good bacteria can have negative health consequences.
- Taking antibiotics can lead to weight gain.
- Wise use of antibiotics often means *not* using them.

I know this list may seem complicated, but the subject of bacteria and antibiotic use is complicated and clouded. All the latest research, as well as expert opinion, seems to be trending in the right direction: We should use antibiotics only in certain situations, we should use them only for a limited time, and we should avoid them at all costs in every other situation.

THE TAKE-HOME

We have lived in the muck and mud for most of our time on this planet. Being dirty was the rule rather than the exception for most of our existence as a species. Our immune system has been learning from, and even working

with, these bacteria for eons. You have so many bacteria inside of you right now that it's valid to wonder whether the bacteria belong to you, or you belong to them. Only a very few bacteria in very few situations are dangerous; those are the bacteria that we should treat with antibiotics.

Any time you take antibiotics for a cold or other viral illness, two things occur:

- The antibiotic has no effect on the cause of your illness or on the number of days you will be sick.
- The antibiotics kill billions of beneficial bacteria in your gut and other places in and on your body. That bacterial slaughter can have a negative effect on your health in many ways.

As we learn more about beneficial bacteria, we're finding that they do everything from protecting our skin from the environment to helping us remain slimmer to keeping us from developing autoimmune diseases.

It's likely that bacteria serve us in hundreds of ways we don't fully understand. When we consider how much we don't know about bacteria, it quickly becomes obvious that we should be exceptionally careful about doing anything that might damage these herds of good and gentle bacteria. Here's an analogy about the effects of taking an antibiotic for every little infection: Imagine you're a farmer who has a fire-ant nest in your pasture. Because the fire ants (a virus) are stinging you and your cows, you hire an expert (a doctor) to get rid of them, and the expert's treatment is to set off a huge cluster bomb (prescribe an antibiotic) in your pasture (your body). When the smoke clears, you would be excited to see that all the fire ants on your farm had been destroyed, but you'd be devastated to see that the expert had also killed all your cattle as well. To add insult to injury, the expert's bomb also knocked over your barn. You don't have to be a wise farmer to know that the cluster bomb is a very bad strategy.



Some doctors are quick to blame their patients for the overuse of antibiotics. However, the truth is that the problem is not with antibiotic overuse; the problem is in the overprescribing of antibiotics. When a worried parent brings a sick child to the doctor for care, it is not the parent's fault if the doctor gives in to the demands for an antibiotic. The parent is only trying to make sure the child's health improves. We wouldn't say that it's the diabetic patient's fault if the doctor prescribes too much insulin, right? We also wouldn't say that it's the drug-addicted patient's fault if the doctor prescribes more narcotics, right? And it isn't the parent's fault if the doctor prescribes the child antibiotics just because the parent has demanded them. The doctor should know when antibiotics are truly called for and refuse to prescribe them whenever they aren't necessary. In my opinion, this is one area where state medical boards should be much more active in policing medical professionals by sanctioning and fining doctors who overprescribe antibiotics.

The best way to be sure your doctor doesn't give you an antibiotic for a viral infection is to not go to the doctor when you have a runny nose, scratchy throat, and a cough. Viruses always cause these symptoms, and there is no magic pill that makes them go away one second sooner than they would without the pill. Your doctor wants badly to help you and for you to see him as being good at what he does. When you see him for a problem he can't help you with, you kick his human nature, which I talk about in [Chapter 2](#), into gear. His inclination is probably to do something rather than nothing, even if the something leads to negative long-term consequences. Doing nothing is very difficult for most doctors to do, even though doing nothing might be the exact treatment you need at the time.

An infection or an illness is often not caused by a bacterial villain; it's caused by a bacterial imbalance that allowed a viral infection to happen. As we learn more about this subject, we're finding that a better strategy than

killing bacteria is to put even more bacteria (good bacteria) into your system. Probiotics are becoming very popular and, although we still have much to learn about the amounts and varieties needed for different conditions, it's becoming obvious that using probiotics is a much more effective strategy than setting off an antibiotic cluster bomb in your body.

You should take a course of antibiotics only if it is certain that a bacterial infection is causing your illness, if the illness probably won't go away on its own, and if the illness caused by the bacterial infection presents a risk of significant danger to you. If you go to your doctor with a runny nose, cough, and low-grade fever, you do not need antibiotics. If your doctor prescribes antibiotics for you, he is hurting your health, not helping it. Only rarely in your life will you need well-chosen, carefully administered antibiotics. If your doctor seems to give you antibiotics almost every time you make an office visit, ask him why it's his go-to course of action and request a copy of the research that backs up his prescriptions.

DO AS I DO

I haven't taken antibiotics in years. Fortunately, I rarely suffer from infections of any kind, but when I do have a viral infection, antibiotics are the last thing on my mind. Probiotics have a daily place in my supplement regimen, and I find this prevents most infections that other people suffer. Only if I had some specific severe bacterial infections would I even consider taking an antibiotic.

HOMEWORK

I'm so glad the table is finally turning on this issue. More and more doctors and experts are realizing antibiotics are dangerous tools that they should use only in specific situations. The following two books describe in elegant detail just how important it is to have the right bacteria. After reading these books, you will protect and nourish your bacteria rather than cluster-bombing them.



Book: *10% Human: How Your Body's Microbes Hold the Key to Health and Happiness* by Alanna Collen, PhD (2016)

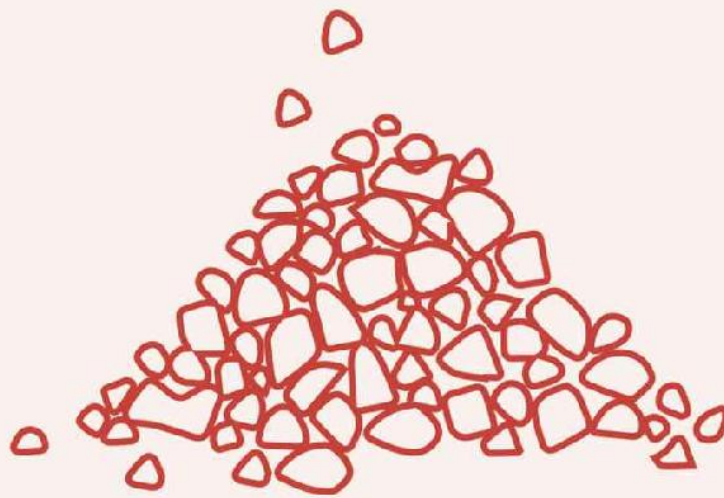
This brilliant book explains, in interesting detail, how many bacteria you contain, all the good things they do for you, and why it's a bad idea to be mean to them. This book is a must-read for all doctors and patients.

Book: *Missing Microbes: How the Overuse of Antibiotics Is Fueling Our Modern Plagues* by Martin J. Blaser, MD (2015)

This book is a very informative work that explains the damage that we have done and all the negative health consequences we experience from overusing antibiotics.

Chapter 13

SALT OF THE EARTH



**We are in the age of M.D.,
medical darkness,
which seeks legislative
protection from the light.**

—James Lendall Basford



THE LIE

Eating salt increases your risk of having high blood pressure, which increases your risk for heart attack and stroke. You should eat a low-salt diet as much as possible to prevent heart disease.

WHY YOU SHOULD CARE

Obviously, you would like to avoid having a heart attack. You would also like to enjoy good-tasting food. The worst possible outcome of this situation would be to endure years of a bland, salt-free Food Pyramid diet and then still have an early heart attack. If eating salt truly does increase heart attack and stroke risk, then we should avoid salt and eat bland foods. If eating salt is safe, then we can relax and salt our food to taste. When you're busy worrying about something that doesn't increase your risk of heart attack, like salt, then you will not be focusing on things that do increase your chances of a heart attack (such as insulin resistance, chronic inflammation, obesity, and alcohol abuse).

SUPPORT FOR THE LIE

The educated opinion of nearly every scientist and doctor in the world is that eating less salt leads to lower blood pressure, thus decreasing your chances of suffering from an early heart attack. For some reason, this medical lie caught on so strongly that, even though there was no real evidence to support it, and little money to be made from it, almost every doctor piled on the bandwagon to bad-mouth salt. Hundreds of articles in every publication, from the most scientific journal to the lowliest gossip rag, supported the idea that eating salt increases your blood pressure and your chances of having a heart attack. However, if you look closely at the scientific literature, even at articles that supposedly proved the salt-hypertension link, it's clear the conclusions were stretched to the limits of believability. Time and again, meaningful research has failed to show any link between enjoying salt with your meals and increased blood pressure (or increased heart attack risk).

THE COMMON SENSE

For all our existence on this planet we have loved salt and have eaten as much as we wanted or could find. All mammals crave salt and will travel

impressive distances to enjoy it. A desire so hardwired into all mammals usually means that we need that substance to survive. Farmers put huge blocks of salt in their barns because the cows love to lick it. The salt is good for cows—not bad. In actuality, it’s very difficult for a normal cow, or person, to eat too much salt. A person with healthy kidneys can easily urinate away excess salt. If you have kidney disease, then you should discuss your salt intake with your doctor.

THE RESEARCH

Hundreds of studies have been done on both sides of this argument, but three large, well-done studies leave little doubt about this lie:

- A 2003 Cochran review of fifty-seven trials stated, “There is little evidence for long-term benefit from reducing salt intake.”
- In 2006, The American Journal of Medicine recorded the salt intake of more than 70 million Americans and compared it to their risk of dying from heart disease over a fourteen-year period. What did the study find? The more sodium people ate, the less likely they were to die from heart disease. (Yep, you read that right).
- The American Journal of Hypertension included a study of more than 8,000 participants. The results reflected that salt had virtually no impact on blood pressure.

So with all this research proving that decreasing salt intake gives no protection from increasing blood pressure or heart attack, why do doctors still tell this medical lie? I honestly have no idea.

THE TAKE-HOME

This medical lie is a fine example of well-meaning experts who believe something, and they try to *help* humankind by pushing that belief onto everyone else. The ideas and research the experts based their assumptions on were flawed; thus, the conclusions were inaccurate. Because of this, doctors give misguided advice to millions of patients. These patients have had to suffer from bland low-sodium diets, which tasted awful, and (according to the one study) actually increased their odds of having a heart attack.

When the experts first published their beliefs about high salt intake, the regulatory bodies (FDA, USDA, AHA, AMA) picked up this lie and ran with it, spreading it even farther than the original research would have traveled. Then every doctor told his patients the lie because he believed he was doing them a favor. Finally, your mom, your brother, and your next-door neighbor were yelling at you every time you picked up the salt shaker. Eventually, as the decades pass, this medical lie will slip into oblivion. Doctors will stop saying it, and, later still, so will everyone else.

Unless you have poor kidney function or significant heart failure, you're free to relax your fears and eat salt to taste on all your food. Humans with healthy kidneys and adequate water intake can eat as much salt as they want. Salt will not hurt them or elevate their blood pressure. They will excrete the extra salt with each full bladder of urine they release.

The human body has very strict mechanisms for keeping the proper amounts of sodium, chloride, and other electrolytes in salt in the bloodstream and tissues. Thinking that eating a little extra salt on your dinner will somehow screw up these mechanisms is silly. Unprocessed sea salt is a little better for you than processed table salt. However, that just means that the processed table salt is less good than the sea salt, but it's not truly bad. The best choice for salt, though, is unprocessed pink or gray sea salt because most of us are deficient in some mineral or another, and the sea salts can help boost these deficiencies. With sea salt, you get all the flavor you want and the multiple minerals your body needs.

If you see your doctor and he tells you to reduce your sodium or salt intake to lower your blood pressure or address some other health issue, please try to take it easy on him. He's repeating a medical lie that's only now starting to die slowly. Many good doctors haven't done the reading they need to be able to see past the lie. You can ask a respectful question about what research he is basing his advice on; that might be enough to motivate him to put on his reading glasses and begin getting up to date. This lie is another great example of how patients can begin to take control of their health, research as deeply as they want into the subject, and begin to take pride in their knowledge and their improving health. Addressing this medical lie with your doctor can be the beginning of a much stronger partnership between the two of you. Either he will do his reading and become a better doctor, or he will be rude to you, which gives you an opportunity to find a new doctor.

DO AS I DO

We always have salt on our table and in our kitchen. We use salt in virtually every dish we prepare. I've never liked the taste of too much salt, but I have no fear of using it. We use unprocessed Himalayan sea salt that we grind ourselves, and we put it in everything. Even if I do develop a blood pressure problem later in life, I will continue to use my sea salt without fear.



HOMEWORK

Salt is necessary for optimized human health, but you will probably need some knowledge bullets in your gun when you attack your doctor with this idea. I'm suggesting two great books and a magazine article that describe all the benefits of eating good salt. The magazine article also includes all the dumb things that experts and government agencies have said and done about salt.

Book: *The Salt Fix* by James DiNicolantonio, PhD (2017)

Dr. DiNicolantonio dives deep into the science to show that salt is a vital, healthy substance for humans, and it can even enhance physical performance.

Book: *Salt Your Way to Health* by David Brownstein, MD (2006)

Dr. Brownstein has been bucking the system for decades. This book is full of great ideas and great information about salt and its health benefits.

Magazine article: “It’s Time to End the War on Salt” by Melinda Wenner Moyer in *Scientific American* (July 2011)

Ms. Moyer gives a great summary of the history of making salt a health no-no and explains how state and federal health experts have bungled this issue. Some of the decisions made at the federal level are embarrassing, to say the least.



Chapter 14

ALL CALORIES ARE NOT CREATED EQUAL



**What some call health,
if purchased by perpetual
anxiety about diet,
isn't much better than
tedious disease.**

—George Dennison Prentice



THE LIE

A calorie is a calorie; whether the source is birthday cake or broccoli. You can eat whatever you want as long as you limit your total calorie intake. You will be slender and healthy by counting calories because all calories are the same. If you want to lose weight, then you should burn more calories than you eat.

WHY YOU SHOULD CARE

If this medical lie were true, it would let you think of junk food and special treats the same way you think of nourishing food. Birthday cake is not a nourishing food, but if you consider the calories in it to have the same effect on your body as the calories in broccoli, then the cake is a valid food choice. According to this lie, your only concern is that you don't go over your total calorie limit each day.

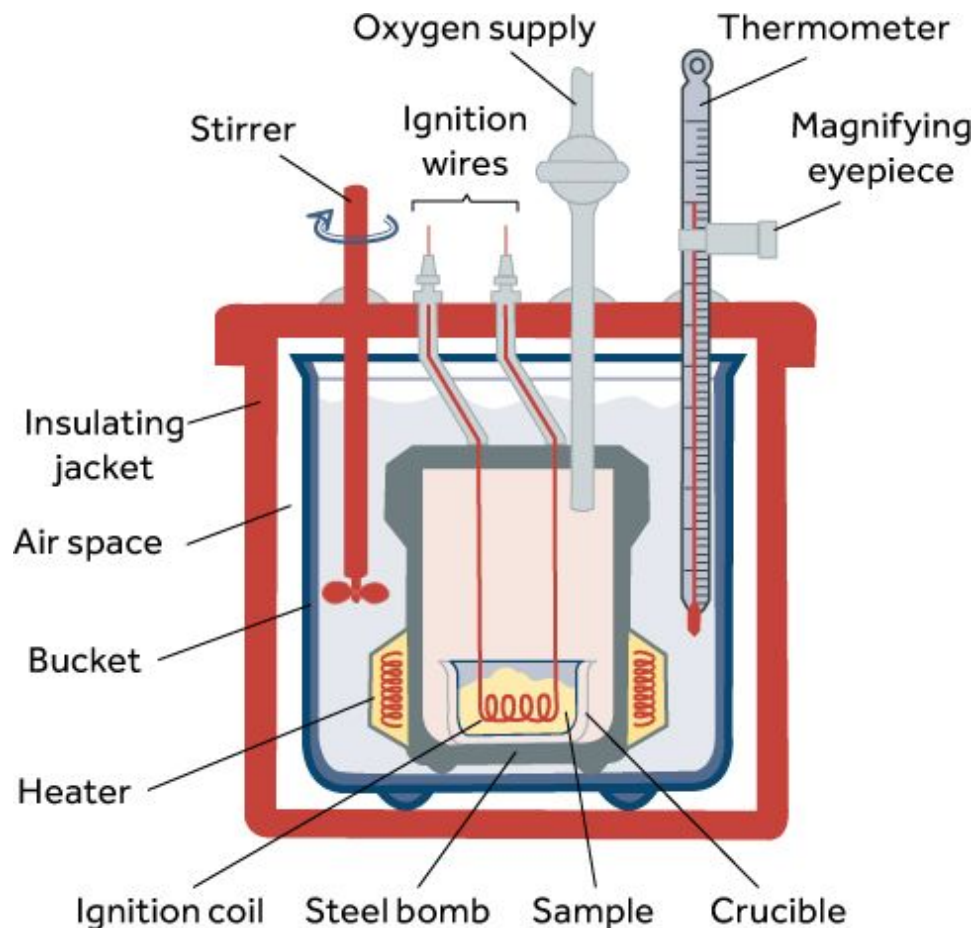
If this lie is true, then you can eat whatever you want as long as you watch your total calorie count. If the total calorie count of the foods you eat is not important, then you should be careful to eat real, whole foods daily and to enjoy treats only occasionally. Good health is built on the foundation of a good diet. We must know what really matters and what things we should spend our money and our effort on if we want to have a strong mind and a healthy body.

SUPPORT FOR THE LIE

Most doctors and magazine articles imply that a calorie from one food is the same as a calorie from any other food. Nutrition experts often tell us that a calorie of cake is no different than a calorie of spinach. Scientists and a few doctors stopped repeating this lie years ago because they had crunched the numbers from large research studies and had shown this belief to be false and not worthy of being repeated. I can find very few medical studies that specifically examine this lie. It is repeated mainly as unsupported, expert opinion. Lazy doctors and concerned family members are now the main repeaters of this medical lie, but it is still out there causing people to make dietary mistakes.

You may have read or heard that fat has more calories per gram than protein or carbohydrates. This statement is true if you burn your food in a little furnace (like the one in the illustration below), but it makes absolutely

no difference as far as your health and weight-loss goals are concerned. Your digestive system breaks down your food biochemically; it doesn't burn your food as a furnace would. Lazy doctors repeat this type of "fact" because they don't know any better and don't make an effort to learn the truth. Many a well-intentioned doctor has instructed their patients that the key to weight loss is to burn more calories than they eat. The doctors tell the patients that a daily *calorie deficit* will lead to weight loss.



THE COMMON SENSE

The way that most of us have learned the calorie paradigm, it would seem to make sense that a calorie is a calorie, no matter what the food source. Scientists came up with the whole concept of a food calorie by burning small amounts of different foods in a little furnace. They measured the escaping heat to determine the calories in the food. The number of calories shown beside a given food has absolutely nothing to do with how the human body

metabolizes the food; it tells you only how many calories of heat-energy were created by burning the food in that little furnace. We don't burn the food we eat; we *digest* it. Common sense really doesn't apply to this lie because the lie itself is nonsensical; we were taught a silly way of describing the *energy* contained in different foods.

The biochemistry used by the human body is extremely complicated. The analogy that we burn the food we eat is a bad one that misleads our thinking on the subject. Don't let a doctor or nutritionist tell you they know everything there is to know about how the body uses our food and stores energy; it just isn't true. The calorie was invented as a way for scientists to talk about the heat energy in food, but it has nothing to do with how healthy a given food is or whether that food will cause you to gain or lose weight.

THE RESEARCH

There is minimal research that supports this lie. Research has been done to determine the calorie count of virtually every food on the planet. However, there is little research showing that the human body cares about the calorie-count of your food, or agrees with the laboratory count of calories in a food or beverage.

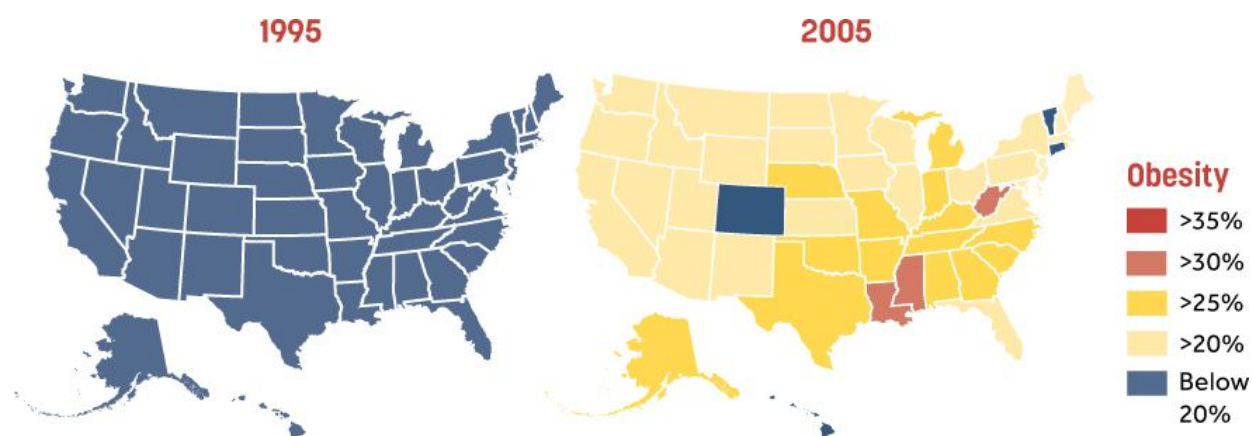
No meaningful research has ever shown that a calorie of cake is the same, from a health and obesity standpoint, as a calorie of bacon or a calorie of artichoke. The "fact" that all calories are equivalent was accepted by the medical and nutrition communities as self-evident, and this medical lie became the basis for all nutritional advice.

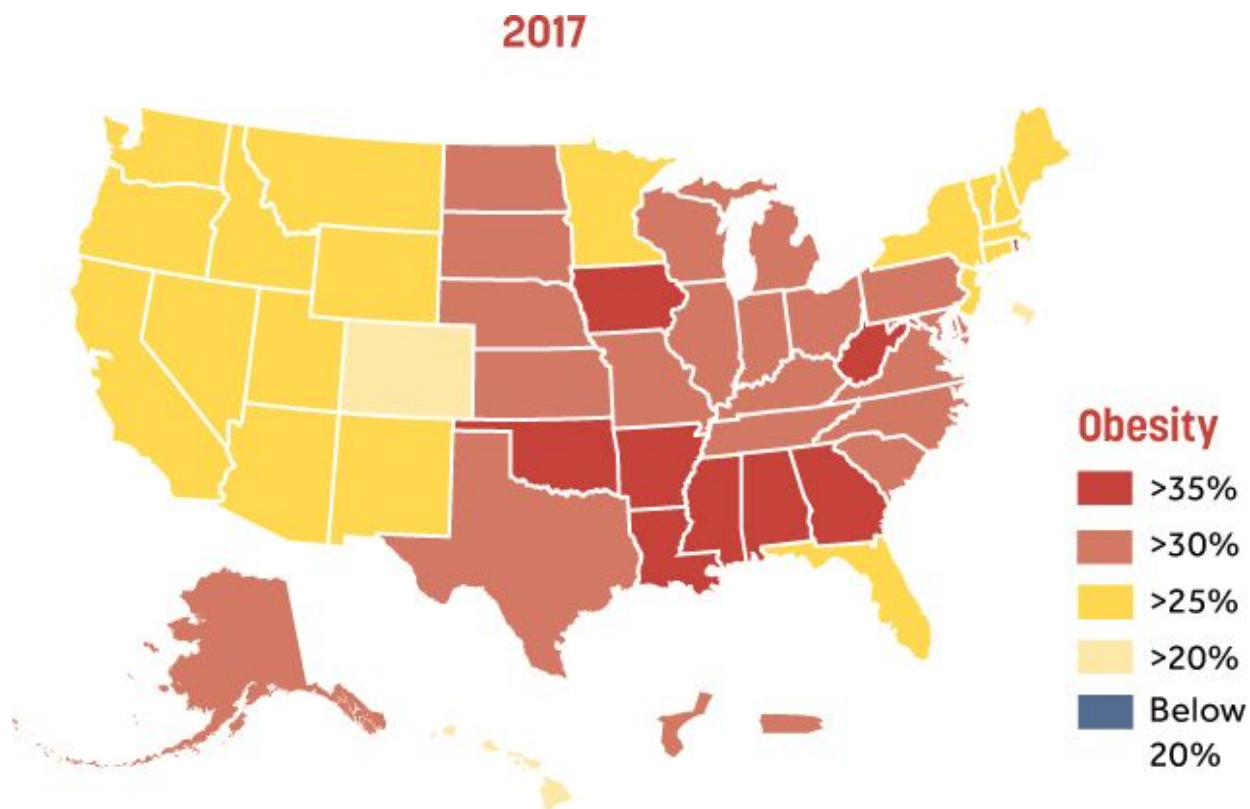
A 2012 article in *JAMA* definitively laid this medical lie to rest. The study analyzed three groups of patients who all ate the same total number of calories daily. One group ate a high-carbohydrate diet, one group ate a high-protein diet, and one group ate a high-fat diet. Which group do you think lost the most weight? Based on what you've learned your whole life, you probably didn't choose the high-fat diet participants, but that group lost more weight than either of the other two groups. Your doctor should have read this article and should know not to be wasting your time talking about counting calories and eating a low-fat diet.

THE TAKE-HOME

Doctors are very busy, and most of them don't understand that being very educated about nutrition is much more important for their patients' health than knowing about the newest pill or shot from Big Pharma. Doctors don't want to be nutritionists; they want to be experts on drugs and medical procedures. Very few doctors seem to realize that most prescription drugs and medical procedures wouldn't be necessary if patients were educated and encouraged to follow a proper diet. I often wonder what the average doctor's answer would be if a patient asked, "Do you think type 2 diabetes is curable?" or "How important do you think nutrition is in preventing heart attack, stroke, and cancer?" I'm afraid the most likely answers would be "No," and "Somewhat important, but not as important as these medications you can take." A good primary care doctor should be an expert on the latest nutritional research and be able to educate his patients about ways to eat to reach and maintain a healthy weight. He should also apply his advice to himself and set a good example for his patients.

A good way to look at this issue is to examine medical advice and obesity rates over the last thirty years. During this time, people have repeated the advice that one calorie is no worse than any other calorie, but the general trend of the population has been to gain weight. The increased obesity of the population doesn't support the idea that a calorie from broccoli is no better than a calorie from a cookie. Counting calories is a complete waste of time. It squanders your valuable energy and motivation by keeping you busy doing something that doesn't help with weight loss, thus almost guaranteeing you will fail.





When the average person becomes motivated to lose weight and get healthier, they usually start counting calories with gusto. They will continue for a month or two, but after seeing minimal results, they will get discouraged and slowly stop trying. (Sound familiar?) Sometimes this poor patient's doctor will make the person feel guilty for giving up, which is outrageous because this very same doctor is the person who gave the patient the bad advice that led to the failure. It's not fair for the patient to be made to feel guilty for giving up on a stupid concept that doesn't work in the first place! If a large part of your current *diet* plan consists of counting and keeping up with calories, then you will ultimately fail. Counting calories doesn't help and doesn't work if your goal is long-term permanent weight loss and improved health. You need to start doing research about how humans should eat and what helps them attain an ideal body weight.

When you're ready and motivated to lose extra weight, you want your effort to produce maximum weight loss. You don't want to put a lot of effort toward this goal to lose a few pounds before gaining them right back. You want to do what will give results immediately and will work permanently. If your doctor tells you the key to losing weight is to cut back on calories and exercise more, please try to contain your anger. Perhaps he has recently been

released from solitary confinement where he was not allowed to read any medical journals for the last few years. You might be able to help him by pointing out an article or two that would bring him up to speed.

Tell your doctor that you're going to eat real, whole foods, and you're going to eat them until you're full. You can explain that a calorie of cake is not equal to a calorie of blueberry, so you plan to avoid the former and enjoy the latter. Please don't waste one second of your time, or one calorie of your effort, worrying about calories. They are irrelevant, and your doctor should know that by now. Weight gain is caused by eating the wrong foods and screwing up your insulin metabolism—not by eating too many calories.

DO AS I DO

Eating large amounts of food-products, which were labeled with a long list of strange ingredients, used to be my usual diet plan. After realizing I was a fat-assed, grouchy, fatigued, heartburn-suffering, runny-nosed doctor who shouldn't be giving anyone health or nutrition advice, I changed all that. Now I rarely eat anything that has more than one ingredient. The ingredients in broccoli are—well, *broccoli*. In our house, eating real, whole foods is the rule rather than the exception. The human body and digestive system knows perfectly well what to do with whole foods. It gets confused by foods that come in cardboard boxes and are made with weird ingredients. Your body tends to put those foods directly on your belly or your butt as fat.

HOMEWORK

The *all calories are equal* lie is so stupid that I'm done talking about it. You need to do some homework on what your body *needs* and how it uses the food you eat. I'm suggesting four great books on this subject. The first three titles are the books that introduced me to this topic, and they changed how I think of human nutrition and how I practice medicine. After you've read these three, you will be smarter than 95 percent of the doctors in the world when it comes to human nutrition.



BOOK: *The New Primal Blueprint: Reprogram Your Genes for Effortless Weight Loss, Vibrant Health, and Boundless Energy* by Mark Sisson (2016)

This book really describes the entire lifestyle you need to look (muscular and fit) and feel (happy and energetic) like a hunter-gatherer. (The copy I initially read was an earlier edition.)

BOOK: *The Paleo Diet: Lose Weight and Get Healthy by Eating the Foods You Were Designed to Eat* by Loren Cordain, PhD (2010)

This is one of the best books I've ever read about human health and nutrition. This author grabbed modern nutrition science by the hair and slapped it silly. Slowly but surely, doctors and experts are waking up to the truth of human nutrition.

BOOK: *Dr. Atkins' Diet Revolution: The High Calorie Way to Stay Thin Forever* by Robert Atkins, MD (1972)

I can't even imagine the cold shoulders and stern looks Dr. Atkins must have endured when he initially promoted his book. He was a doctor who thought outside of his box, and he should be knighted or sainted for shifting the paradigm as much as he did. He was a true revolutionary, rest his soul.

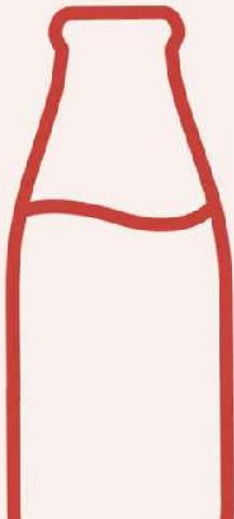
Book: *Good Calories, Bad Calories: Fats, Carbs, and the Controversial Science of Diet and Health* by Gary Taubes (2008)

The book that first revealed the truth about calories and weight loss that has been known for decades but forgotten by most doctors.



Chapter 15

DOES TOO MUCH CALCIUM CAUSE KIDNEY STONES?



**The art of medicine
consists in amusing the
patient while nature cures
the disease.**

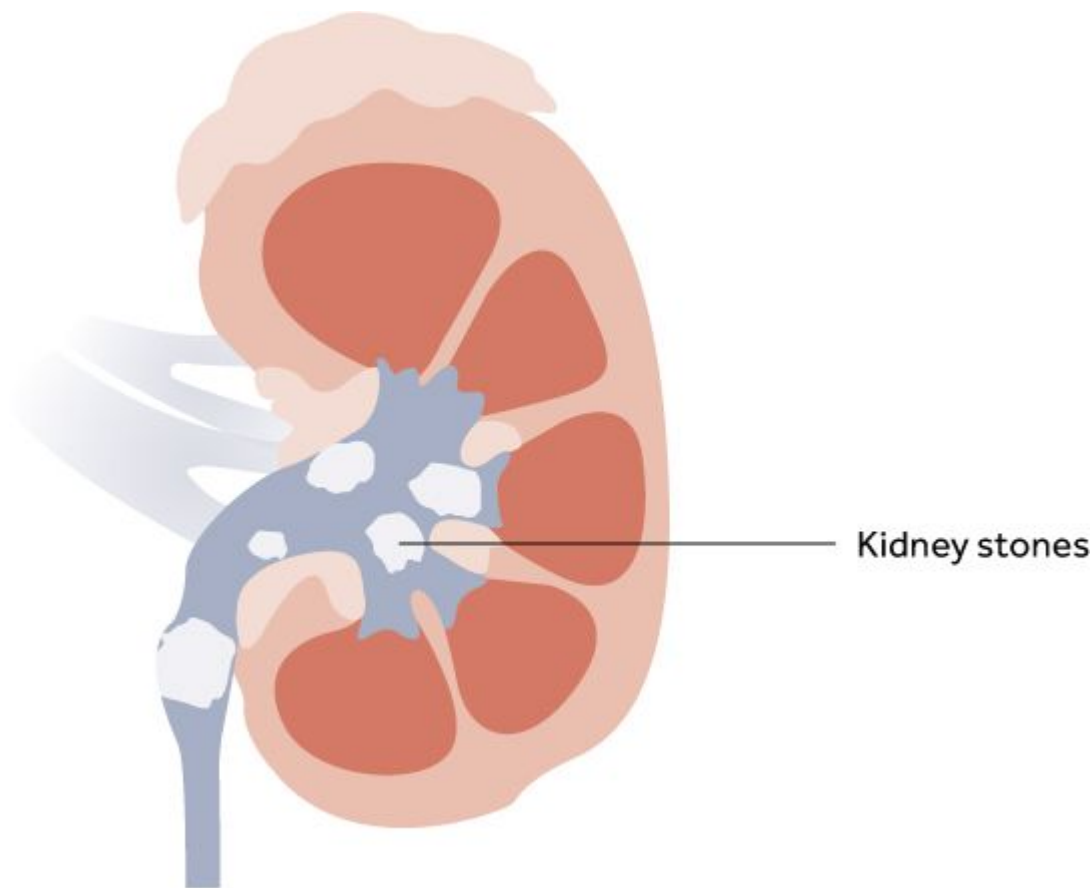
—Voltaire



THE LIE

Eating or drinking too much calcium can lead to kidney stones. Also, if you've had a kidney stone, you should decrease your calcium intake so you don't get another.

WHY YOU SHOULD CARE



Large kidney stones are, without doubt, one of the most painful things the human body can experience. Any time a woman describes a pain as worse than childbirth, you better bet you don't want to experience it. I've had multiple women over the years tell me their kidney stones were much more painful than the worst of their labor pains. As a man, all I can do with this information is place the pain at about twenty-five on a ten-point scale and pray I never experience it. No woman has ever described any other pain to me using the childbirth analogy, even when she's had multiple broken bones. So, if high-calcium foods increase your risk of kidney stones, then

maybe you should cut down on eating them. But if high-calcium foods don't increase your kidney stone risk, then you can enjoy them as much as you want.

SUPPORT FOR THE LIE

Many people on the street and some doctors will repeat this medical lie as truth. There is absolutely no research showing that high-calcium foods in your diet increase your risk of a kidney stone. There is some mediocre research showing a possible relationship between taking large doses of calcium supplements and developing kidney stones, but the jury is out on this theory until someone performs a meaningful study.

THE COMMON SENSE

Because most kidney stones consist of mostly of calcium, it seems to make sense that eating too much calcium might increase your chances of having a kidney stone. Calcium is vital to building bone and hundreds of other bodily functions, so it stands to reason that you should make sure you get plenty of it. Calcium levels in the blood and urine are tightly controlled by the body's mechanisms. Calcium metabolism is too complicated to be boiled down to a summary as simple as "eating too much will cause your body to produce stones that result in the worst pain known to humans."

THE RESEARCH

No research has ever shown that high levels of calcium in your food and drink increases your risk of a kidney stone. Also, no study has ever shown that those who have had one kidney stone can decrease the risk of having another stone in the future by lowering their calcium intake. A study presented at the ninety-fourth meeting of The Endocrine Society showed a possible link between taking a calcium supplement (pill) and increasing risk of kidney stones, but the evidence was far from convincing.

THE TAKE-HOME

Calcium in your diet does not cause kidney stones. If you have a kidney stone at some point, it does not mean that you should avoid foods that are

naturally high in calcium. You can decrease your risk of having a stone, but you can't do it by avoiding calcium in your diet.

For a few years, it was very popular, especially for women, to take a calcium supplement. Although this was probably unnecessary and probably didn't increase their bone strength, we didn't see a sudden uptick in kidney stones in women. The nutrient in which most women are deficient and that most likely will increase bone strength (and help the body's biochemistry in hundreds of ways) is vitamin D3.

Most people get enough calcium in a healthy diet, but it is almost impossible to get enough vitamin D3 in a modern diet. We are told to hide from the sun because too much sun causes cancer, but without exposure to the sun, you're not getting vitamin D the way nature intended. Therefore, most people have to take a vitamin D3 supplement daily. Don't worry about too much calcium in your diet causing kidney stones, but do ask your doctor to order a Vitamin D-25 level for you. Checking your vitamin D level is important.

If your doctor tells you to decrease your calcium intake to keep you from making kidney stones, you should respectfully tell him you would like a copy of the research upon which he's basing his advice. This request will most likely fluster him and give you the perfect opportunity to start working on an improved partnership with him.



DO AS I DO

I've never had a kidney stone, and I want to keep it that way. Eating a natural whole food diet gives me plenty of calcium (from kale, sardines, broccoli, okra, and almonds). Drinking milk isn't necessary. I also plan to take a vitamin D3 supplement daily as needed until I've saved enough money to move to Key West, where I'll produce plenty of vitamin D from sun exposure, as nature intended.

HOMEWORK

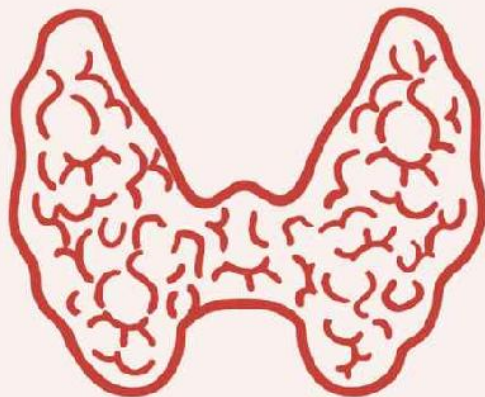
Because the real problem isn't about getting enough or too much calcium, you should do homework about vitamin D instead of reading about calcium. I'm suggesting a web page that will make you an expert on vitamin D, which is a very important nutrient most of us don't get enough of.

Website: *Vitamin D Resource Page* The Vitamin D Council

The Vitamin D Council has great information about vitamin D at <http://bit.ly/VitDFAQ.XBPRRGhKiUk>.

Chapter 16

YOUR TSH IS NORMAL, SO YOUR THYROID IS FINE



**It is easy to get a
thousand prescriptions
but hard to get one
single remedy.**

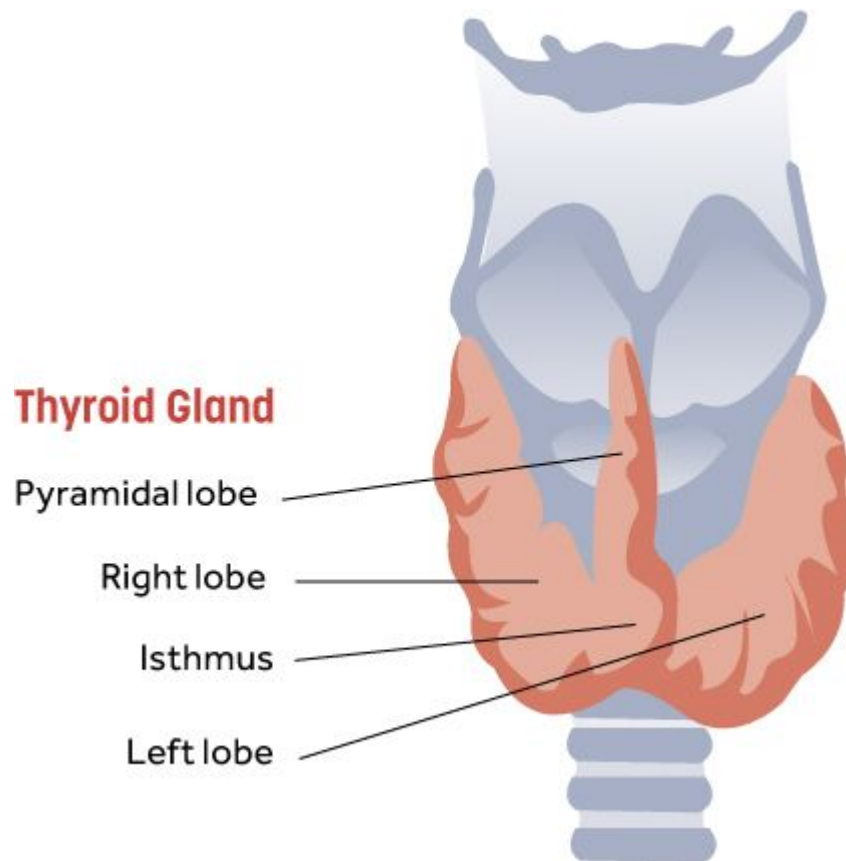
—Chinese proverb



THE LIE

TSH (thyrotropin stimulating hormone) is all you need to have checked to find out whether your thyroid is functioning normally. If TSH is within normal limits, then your thyroid gland is fine, and your symptoms are all in your head.

WHY YOU SHOULD CARE



The thyroid gland and the hormones it produces affect virtually every biochemical reaction in your body. If your thyroid doesn't function properly, the result is fatigue, weight-gain, memory-loss, disease, and even early death. If the TSH test is the only lab test that needs to be checked to assess thyroid health, then so be it. If, however, a full panel of thyroid lab work and the patient's symptoms and signs need to be considered before the doctor makes a diagnosis, then let's make sure to check all of it.

SUPPORT FOR THE LIE

It is the opinion of almost every thyroid specialist (endocrinologist) that if your TSH level is within normal limits, then your thyroid is fine. Recommendations from endocrine societies recommend the TSH test as the only test needed to screen the thyroid gland. All doctors were, and still are, taught this lie in medical school and residency, and they haven't thought much about it since. The TSH test is quick and easy to perform, and the results appear to be undeniable black and white. Very few doctors have any doubt in using the TSH test for diagnosing thyroid disease.

THE COMMON SENSE

Given that the thyroid is known the world over as the master gland of the human body, it would seem that proper diagnosis and treatment of thyroid conditions is vital to long-term health and happiness. Way back in the 1970s, the TSH level became the standard way to test the thyroid. For some reason, doctors (even so-called thyroid specialists) want to bet your thyroid health on this forty-year-old test.

TSH is not even a thyroid hormone; it's a hormone produced by the anterior pituitary gland in the brain. The pituitary produces TSH as the way of telling the thyroid gland to produce more thyroid hormone. When the thyroid hormone level circulating in the blood is at the proper level, it feeds back to the pituitary gland, telling it to stop producing TSH. There are multiple places in this feedback loop where something can go wrong but remain completely undetected in the lab work if your doctor checks only your TSH level.

An article by Colin M. Dayan, FRCP, in the 2001 *Lancet* discussed this potential problem and suggested that at least TSH, FT3, and FT4 should be checked to minimize the chances of overlooking hidden disease. FT3 is free T3, the active form of thyroid hormone that circulates in the blood, and FT4 is free T4, the storage form of circulating thyroid hormone. Even though this doctor told the medical world via a respected medical journal that checking just the TSH was not enough, hard-headed doctors kept right on checking only the TSH.

THE RESEARCH

Research supporting this lie is tenuous at best. When the TSH test became available, doctors were excited about having a fast and easy thyroid test. They basically forgot how to use their critical judgment and physical examination skills where the signs and symptoms of thyroid disease are concerned. They started to blindly trust this one test. Authors of research papers often initially imply that the TSH is all that needs to be checked, but then they waffle later in the article by mentioning something like “the TSH test’s weaknesses should be kept in mind.” Many doctors have stopped reading before they get to the second part. Therefore, they falsely think the TSH test is the only test needed to diagnose thyroid disease.

When any test is discovered and marketed as the new gold standard, it tends to dull the critical thinking of doctors. When all the advertising and the doctors with the longest white coats say the test works, regular doctors begin to blindly accept the advertising as unquestionable truth and stop thinking for themselves. This sort of error has often happened in medicine—so often that you would think doctors would be wary of blindly trusting a patient’s health to new tests. No research I know of has ever attempted to prove that the TSH test is the only test needed to check the state of your thyroid health, yet doctors keep acting as if it is the only thyroid test needed.

THE TAKE-HOME

Any time a test or treatment is called the *gold standard* in medicine, it tends to make doctors mentally lazy. This label leads them to think everything worth knowing about a topic is already known, and there is no need for further thought or effort. The TSH test is one such gold standard. The assumption that one test is sufficient for diagnosis and management often makes doctors look foolish, and causes patients to suffer. Doctors use the TSH test for everything from a physiological marker of thyroid function to a guide for initiating and monitoring thyroid medication dosages. It is an inadequate test for all these uses.

Most doctors have no idea how the normal range of a lab test is determined or what can falsely elevate or depress the measured level of a test. Before the TSH test became widely available, doctors listened to and examined their patients for symptoms and signs of thyroid disease. If a patient had severe fatigue, weight gain, and constipation and was losing the

outer one-third of her eyebrows, doctors diagnosed the patient with hypothyroidism without needing the TSH test.

Now, because a gold standard has been announced for diagnosing thyroid issues, most doctors have stopped looking for physical signs and symptoms of thyroid disease. Instead, they only check a patient's TSH level instead. Another serious problem with this test is that the TSH level can be affected by a patient's smoking, sickness, stress level, or activity level (such as when the patient works out before having the lab work done). Most doctors have no idea that a patient's TSH level can be affected by so many things or that the level can change substantially over the course of a single day.

Whenever a patient makes time in a busy schedule to make an appointment with the doctor because fatigue, weight gain, mental cloudiness, and other symptoms have gotten so bad the patient can hardly function, doctors should listen to the symptoms and look for the signs of thyroid disease. In other words, the doctors should take the patients seriously. Next, the doctor should order a full thyroid panel that checks TSH, FT3, FT4, RT3, TPO, and TGA. There are several other non-thyroid tests the doctor needs to check to fully investigate possible thyroid problems. You can find the complete lists of tests in the book and website listed in the "Homework" section at the end of this chapter.



Many doctors have told patients that their thyroids were fine after a test returned a normal TSH value even though the patients have had serious

thyroid disease and severe symptoms. When the TSH test is the only thyroid test the doctor checks, patients can have their TSH level come back *normal* for years before a doctor finally diagnoses them with thyroid disease. Many of these patients start taking an antidepressant pill. Some are told to exercise more and eat less, or they're told that their suffering is all in their head. I consider this very disrespectful and poor medical practice; it's malpractice, in fact.

To say the TSH test is the only test needed to diagnose thyroid disease is a lazy medical lie. If you have multiple thyroid symptoms, and a doctor has said that your *lab work* is normal, ask for a copy of the results to see what the doctor checked. (Your lab results belong to you, not to your doctor, so there's no reason you shouldn't be allowed to have a copy.) If the doctor and lab tested only the TSH, then you have the choice of going back to try to educate your doctor or finding a new doctor who will listen to you and take your symptoms seriously. Spend some time educating yourself using the two resources at the end of this chapter to learn about all the testing and thought doctors must do to provide an accurate diagnosis of thyroid disease.

DO AS I DO

Because thyroid symptoms can be rather subtle, I have my thyroid tested annually (if not more often). I don't stop with the TSH test; I check a full thyroid panel. I also make sure my wife has her levels checked. Thyroid health is closely linked with eating an organic, whole food diet and avoiding as many environmental toxins as possible, so that is how we eat and live.

HOMEWORK

It seems that most doctors refuse to do their homework on thyroid disease and thyroid testing, so you will have to do it for yourself. Here are two great places to begin learning about the complicated gland that is your thyroid.

Book: *The Paleo Thyroid Solution: Stop Feeling Fat, Foggy, and Fatigued at the Hands of Uninformed Doctors* by Elle Russ (2016)

The author was a patient who was so mistreated by multiple doctors that she began a personal study and taught herself to treat her thyroid condition.

This book includes an in-depth commentary from integrative physician Gary E. Foresman, MD.

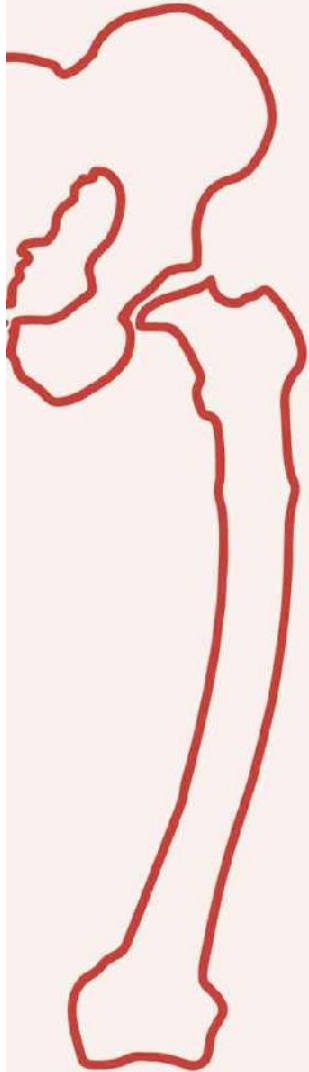
Website: *StopTheThyroidMadness.com* by Janie Bowthorpe

A couple of hours of reading and taking notes on this website will make you smarter than the average doctor is about hypothyroidism. The site also includes more than a decade's worth of patient experience with both testing and treatment of thyroid conditions.



Chapter 17

**IF YOU DON'T
HAVE RICKETS,
THEN YOUR
VITAMIN D
IS NORMAL**



**A smart mother makes
often a better diagnosis
than a poor doctor.**

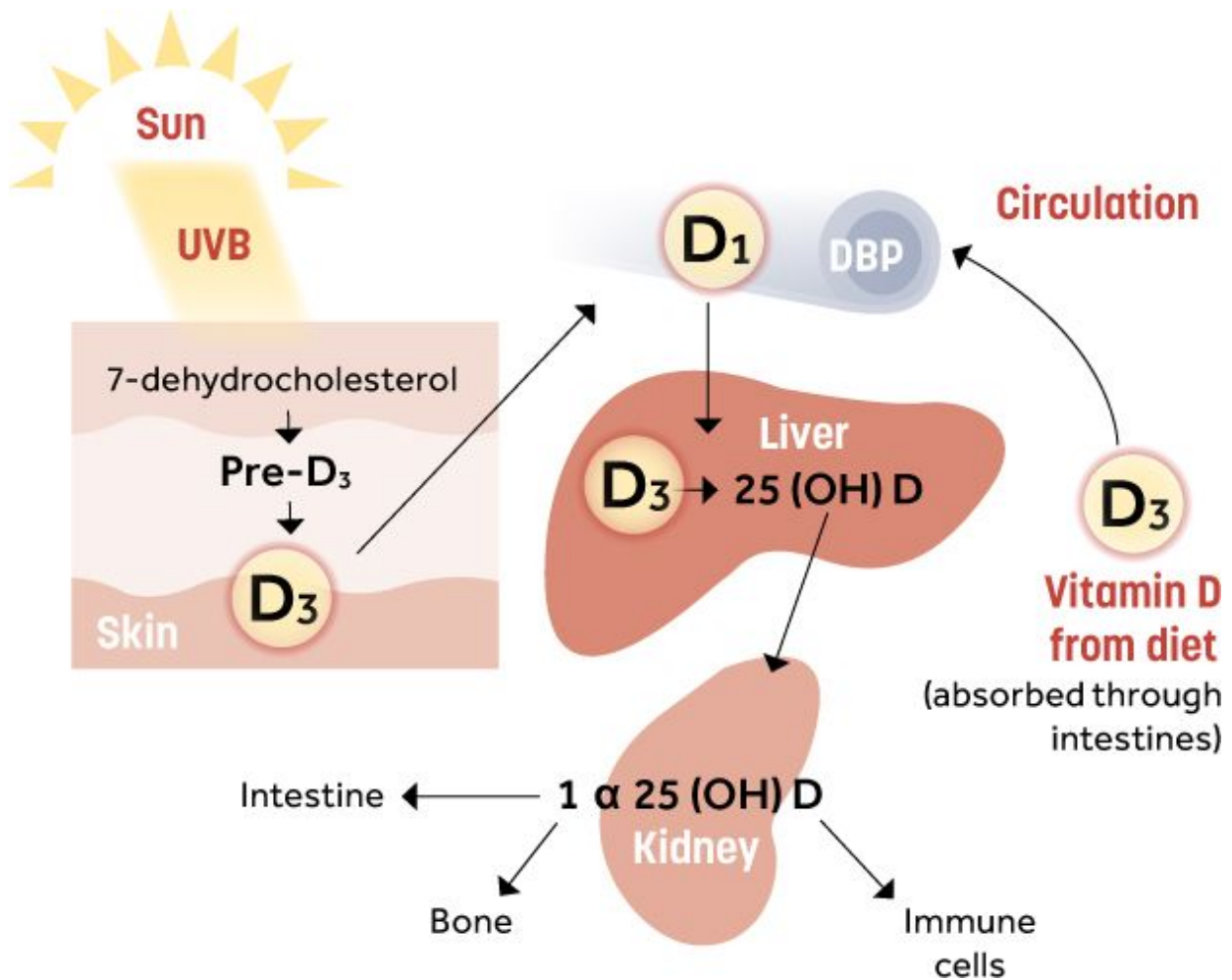
—August Bier



THE LIE

You get enough vitamin D from your diet. The fact that you don't have rickets (weak, bending bones in a child) or osteomalacia (weak, painful bones in an adult) is proof that you are getting enough vitamin D, and you don't need to take a vitamin D supplement.

WHY YOU SHOULD CARE



Vitamin D is not just a vitamin; it's a prohormone, which is an inactive hormone that must be activated in specific cells through a series of activation steps. It is involved in thousands of biochemical reactions in your body. If it does help your body in thousands of ways, and perhaps even prevents cancer, then you should make sure that you get enough vitamin D every day. If you need only enough vitamin D to prevent rickets and

osteomalacia, then you are free to continue not caring about your vitamin D level.

There have been several small and medium research studies that demonstrate that getting more vitamin D could benefit health in many ways, but not many doctors seem to care. The USDA was content for decades to recommend the tiniest daily amount of vitamin D possible. Recently, the vitamin D RDA was increased by a small amount, and experts have started to recognize that different types of people (pregnant woman, children, and the elderly) need more vitamin D than other people. However, the current recommendation remains substandard for optimum health and disease prevention.

THE COMMON SENSE

Vitamin D is very important to hundreds of biochemical functions in the human body—so important, in fact, that our bodies learned thousands of years ago to make it from our exposure to sunlight. That seems like a pretty big deal. Over the last century, we have moved most of our activities indoors, out of the sun, and we've drastically cut the amount of fat we eat (fish oil, lard, and bacon are great sources of vitamin D), so our average vitamin D level has been steadily falling.

Vitamin D is responsible for so many beneficial things in the human body that it deserves a book of its own. Most of us know that vitamin D helps us absorb calcium to help keep our bones strong. However, an increasing number of experts are starting to recognize that this may be the least of its benefits. Vitamin D appears to have great benefits for your immune system, mood, heart health, and even sexual function. It is becoming clear that taking the minimal amount to keep rickets and osteomalacia away isn't sufficient for optimal health.



THE RESEARCH

There are two groups of thought, and two types of research on this topic. One set of experts focuses only on the minimal amount of vitamin D needed to avoid severe deficiency. These experts focused their research on this topic, and they didn't do research studies that involved taking more than 1,000 daily IU. (IU stands for international units, which is the measurement unit for vitamin D.) These studies are what medical schools teach; therefore most practicing doctors know only about these minimum requirements.

More recently, another set of researchers have found that higher levels of vitamin D can be very beneficial for many different areas of human health. Research studies and reviews have shown a correlation between higher vitamin D intake and reduced rates of cancer, type 1 diabetes, multiple sclerosis, skin cancer, and other diseases. The literature suggests that it's very hard to harm yourself by taking too much vitamin D. One case study followed an individual who accidentally took more than 100,000 IU daily (from a mislabeled supplement) for months. Although he suffered nausea and body aches while taking this much vitamin D, as soon as he discovered his overdose and discontinued taking that quantity, he went right back to normal with no long-term consequences.

THE TAKE-HOME

In 2007, I read an article about vitamin D that stated there was a rampant vitamin D deficiency in most people. I didn't find this article in a respected medical journal. I found it on an alternative health website. I was very skeptical of this information because I hadn't read anything about this deficiency in more official medical literature. To do some research on my own, I started checking vitamin D-25 levels (not the 1,25 level) in some of my older patients, who were at risk of osteoporosis. Vitamin D-25 is a much more accurate test and is the only one that should be checked.

To my surprise, I found that seventy-two patients out of one hundred had a vitamin D-25 level below 30 ng/mL. Normal is 30 ng/mL to 100 ng/mL. In my opinion, the optimal level is 50 ng/mL to 100 ng/mL. That means that a total of 72 percent of my elderly patients were deficient in this vital substance, and I had been completely unaware of the situation! I hadn't

been taught about the importance of checking vitamin D-25 levels and was blind to the deficiency in my patients. I began ordering vitamin D-25 levels for younger and younger patients, and I found many of them also were deficient in vitamin D. I was mortified by this discovery, and I immediately read everything I could find about vitamin D. I began recommending that all my patients take a vitamin D3 (not vitamin D2) supplement.

I spoke to several of my doctor friends about my discovery. They told me that they never checked vitamin D levels in their patients, and they seemingly had no interest in starting to test. The more I read about vitamin D, the more I was convinced that it was a vital ingredient for overall health. However, I felt like a lone voice in the wilderness. Most patients would have no idea why they should take vitamin D because the media had never covered this issue, and other doctors wouldn't have brought it up. In some cases, I had patients whom I had referred to various specialists come back to see me who reported that the specialist had told them to stop taking the vitamin D supplement I had recommended. The specialists said the patients didn't need the supplements and might experience a dangerous overdose.

These specialists usually offered this *advice* without checking the patients' vitamin D levels. The doctors didn't base the recommendations on research or critical thinking. When I did more investigation into the research on vitamin D overdoses, I discovered that not one serious overdose had ever been reported. None. Zero. Zip. Zilch. Although people had accidentally significantly exceeded the RDA for long periods of time, there was not a single death or serious injury. So, if your doctor warns you against taking more than 1,000 IU of vitamin D, you can be sure he has read nothing new on the subject since he was in medical school.



DO AS I DO

As I said in an earlier chapter, I play in the sun without sunscreen as often as possible. I eat lots of pastured fatty foods like butter, egg yolks, and pork. I

also take 5,000 to 10,000 IU of vitamin D3 every day as needed to keep my level above 50. I check the vitamin D level in my blood twice yearly, and the results show I am not close to overdosing. I will always take a daily vitamin D supplement unless I move closer to the equator where the sun is stronger.

HOMEWORK

There are several books about vitamin D therapy, how much you should take, and why supplementing vitamin D is important. However, I'm recommending a website because it's a great place to start your vitamin D education. Armed with this information from this site, you can discuss your vitamin D needs with your doctor.

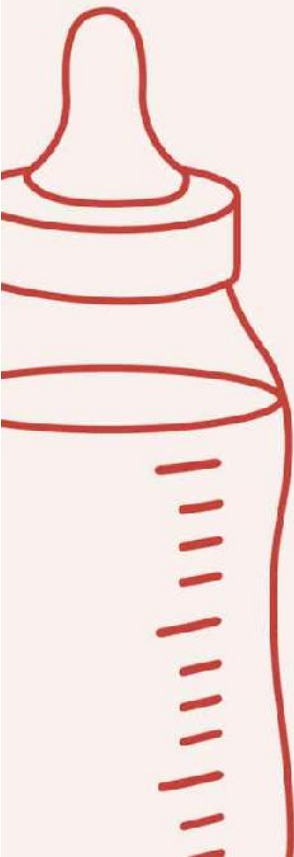
Website: *Vitamin D Resource Page* The Vitamin D Council

Visit <http://bit.ly/VitDFAQ> for a very useful resource for learning about vitamin D and all of its powers to prevent and heal.

Chapter 18

BREAST MILK

**DOESN'T CONTAIN
EVERYTHING
A NEWBORN
NEEDS?**



**It is important to keep in
mind that our bodies must
work pretty well, or there
wouldn't be so many
humans on the planet.**

—Ina May Gaskin



THE LIE

Human breast milk is deficient in vitamin D. Babies who are exclusively breastfed should be given vitamin D drops.

WHY YOU SHOULD CARE

We want our babies to receive the best nutrition possible to give them a head start on a healthy, happy life. If breast milk is truly deficient in vitamin D, then we should give vitamin D drops to babies who are exclusively breastfed. If breast milk contains everything a baby needs, then let's not tell new mothers that their breast milk is deficient and that Big Pharma needs to help nourish the babies.

SUPPORT FOR THE LIE

Every medical and nursing student has been taught this medical lie for as long as any of us can remember. Studies that examine the nutrition in breast milk did indeed show it had almost no vitamin D at all. With this seemingly straightforward information, it seemed clear that infants who were to be exclusively breastfed should receive supplemental vitamin D drops to make up for this shortfall. This lie is ingrained in medical education and will probably take decades to erase.

THE COMMON SENSE

One of my first *what-the-hell?* moments in medical school came when I heard this lie. I've always been of the opinion that the Creator and Mother Nature have taken care of everything. The job of doctors is to correct the little errors that occasionally happen and fix the trauma we humans inflict upon ourselves. My memory is that my medical team (which was our attending physician, a senior resident, two interns, and three of us lowly medical students) was on the labor and delivery ward one early morning. We had been on call all night, delivering babies and assisting with cesarean sections. All of us were exhausted. The intern was presenting a patient's information to the team and was going over the baby's regimen.

He mentioned vitamin D drops. One of the medical students (not me—I was too tired to ask questions that day) asked why the newborn was getting these drops. The senior resident, who was annoyed by all medical

students, told us that all babies needed vitamin D drops because there is no vitamin D in breast milk. This statement woke me up. I glanced at our attending physician, who I was sure would correct the resident, but he only nodded in quiet agreement. “How can that be?” I thought to myself, although I was too tired to speak out. When did mothers stop putting vitamin D in their breast milk? I was about to ask that question, but by that time we had moved on to the next patient. I filed the question away for later research. Although I didn’t have time to research the issue then, I kept returning to the thought. Something about it just didn’t seem right.

Vitamin D drops have been around for less than one hundred years, so it makes one wonder how humans could have survived for thousands of years without giving breastfed babies (which would have been all babies for centuries) vitamin D drops. Maybe vitamin D is not that important? No, research continues to show that it’s vital to thousands of biochemical reactions in the bodies of babies and adults. It is both a prohormone and a vitamin. We must have this essential substance, so how did babies obtain vitamin D in the days before the invention of vitamin D drops? Were mothers of the past somehow able to produce vitamin D in their breast milk, whereas modern moms had lost this ability? It turns out that *is* the explanation, and the reason seems obvious when you know it.



THE RESEARCH

As I said earlier, about seventy years ago, research started showing that human breast milk contained almost no vitamin D. This discovery has never

been disputed, and apparently decades passed before anyone questioned the reason. However, Professor Bruce Hollis, PhD, thought he might have a theory about why mothers seemingly let their infants down in such an important way. He decided to give breastfeeding mothers supplemental vitamin D to see if the supplements would enable them to produce vitamin D in their milk. Hollis began by giving the mothers 2,400 IU of vitamin D daily (much more than the RDA for breastfeeding mothers). Even after supplementing with this seemingly high amount, the mothers still produced so little vitamin D in their milk that the ethics committee stopped the study for the safety of the infants.

Hollis then decided to give the mothers 6,400 IU of vitamin D daily, and, amazingly, the mothers in the study started excreting vitamin D in their milk! In fact, they produced so much vitamin D in their milk that their infants didn't need the supplemental drops. They were getting everything they needed from their mothers, just as it should be. Hollis published his study in 2015, and it should have jerked the entire medical community awake, but it did not. Very few obstetricians, pediatricians, or family doctors even know about this study, much less use its results to counsel their patients. This study was large, well-managed, randomized, and double-blinded. There can be no doubt about the truth of its findings, yet the results are helping very few patients.

THE TAKE-HOME

Breast milk is more than a liquid; it is a living tissue custom formulated by each mother for her baby. Hundreds of years ago, breastfeeding mothers got plenty of vitamin D from the sun and their high-fat diets. Therefore, they produced plenty of vitamin D in their breast milk for their babies. My feeling about this had been right all along. When the female body has proper nourishment and exposure to the sun, it will produce every single vitamin, mineral, and nutrient an infant needs to grow and succeed. The reason why the previously mentioned studies had shown low levels of vitamin D in human breast milk was because those modern women, who lived indoors and ate lower-fat foods, had very low levels of vitamin D in their blood. They were, therefore, not able to produce more for the breast milk for their babies.

I'm still flabbergasted when I think of the intelligent professors and doctors who taught my classes at the university. Why had none of them ever

thought about, or questioned, this seeming deficiency in the makeup of breast milk? They were evidently too busy and/or not willing to make negative waves by questioning the traditional teaching. Every day, doctors are busy interacting with an endless cycle of miraculous biochemical events in human metabolism. Doctors are used to the human body healing itself, growing, reproducing, and doing many other amazing things. Why would doctors be comfortable thinking that this same human body might forget how to produce one of the most important vitamins in human breast milk?

This lack of logic should have immediately raised red flags about the deficient amount of vitamin D in the mothers' diets, but it didn't. As usual, instead of fixing the underlying problem or deficiency, doctors and Big Pharma decided to prescribe vitamin D drops to the infant to fix the problem. But what if a mother couldn't afford the drops or didn't want to administer them for the time she was exclusively breastfeeding her baby? Wouldn't it have been more elegant to give the mother the right amount of vitamin D? Then, not only would the mother have had the vitamin D she needed for her body but she could have effortlessly passed vitamin D to her baby every time she breastfed. Instead, we find ourselves in a situation in which busy mothers often forget to get the drops at the pharmacy or forget to give the drops to their babies every day. Thus, their babies have an increased risk of diseases, such as rickets. When these babies are grown up, they will most certainly suffer from vitamin D deficiency.

Any time experts say that human bodies don't make or do something we need, we should be immediately suspicious. Unless they can convincingly explain why this is the case, you should start doing research for yourself. Women who are trying to get pregnant should take 6,000 to 8,000 IU of vitamin D daily from the time they start trying to conceive until the day after they wean their baby from breast milk. That supplementation will take care of the baby's needs. Since the modern diet is currently so deficient in vitamin D, all of us should probably take that amount every day regardless of whether we're breastfeeding a child.

DO AS I DO

I get excited every time I explain to one of my pregnant patients that if she takes a vitamin D supplement, then she can make everything her new baby needs to thrive and be healthy. Make sure any of your friends or family who

are with child know they can make everything their baby needs. A baby doesn't need anything a mother can't provide.



HOMEWORK

Once you understand this topic, it's such a no-brainer that no further study is needed. I think you deserve the day off from homework.

Chapter 19

GOD MADE THE SUN, AND GOD MADE YOU



**I think you might dispense
with half your doctors if
you would only consult
Dr. Sun more.**

—Henry Ward Beecher



THE LIE

Exposure to sunlight causes skin cancer. To decrease the risk of skin cancer, you should stay out of the sun as much as possible. If you must be in the sun, then you should wear lots of high-SPF sunscreen to protect yourself. You should even wear sunscreen when you're inside if you will be exposed to sunlight from windows.

WHY YOU SHOULD CARE

Any time medical science tells you to avoid nature or something natural, your BS sensor should sound an alarm. If we're now considering the sun to be dangerous, you should protect yourself from it, and there better be some darn good research to back up this claim. However, if there is no meaningful research to support this "dangerous sun theory," then you may continue to play in the sun and use it to make vitamin D as humans have done for thousands of years.

SUPPORT FOR THE LIE

The American Society for Dermatologic Surgery (ASDS) and the American Academy of Dermatology (AAD), the two leading academies of skin doctors in the United States, have an endless supply of brochures that repeat this medical lie. These societies recommend that you wear sunscreen to prevent skin cancer (even indoors!). You can find thousands of pages of "patient education" on this topic on the societies' websites.

Almost every doctor you ask tells you to limit your sun exposure and to wear sunscreen whenever you will be in the sun; in some cases, doctors say to avoid sunlight altogether. Some studies seem to show a link between sun exposure and certain types of skin cancer. However, most of these studies are poorly designed (for example, one was done on donated baby foreskins that were no longer attached to the baby), or the conclusion of the study does not logically follow from its findings.

THE COMMON SENSE

Humans have been playing and working in the sunshine for many thousands of years. Sunlight is as natural as, well... sunlight! Making the claim that exposure to sunlight causes cancer would require exactly the same stretch of

the imagination as saying that drinking pure mountain spring water causes cancer or that eating organic green plants causes cancer. Human skin has been exposed to sunlight for so long that it has learned to use sunlight to make a vitamin/prohormone (vitamin D).

Despite these facts, a few decades ago doctors *discovered* that somehow the sun is dangerous to human skin, and we should protect our skin from the sun's damaging effects. On the commonsense level, this lie is ridiculous. In our modern society, in which we often believe things that make no sense and repeat them as truth, this lie has caught traction and become the official stance of the skin specialists. It has become the mantra of skin-care experts everywhere. From dermatologists to sunscreen makers, everyone who can make a living promoting the dangerous sun theory is doing so.

For thousands of years, no one gave a second thought to sunshine being the cause of any disease. However, in the last forty years, some of the smartest among us have *discovered* that the very thing that makes all life on Earth possible is now also the leading cause of skin cancer. Life wouldn't exist on Earth if it were not for the sun, so it strains believability that this same sun is now dangerous to life.



THE RESEARCH

There is no major scientific study that proves conclusively that exposure to sunlight causes skin cancer. You're probably thinking, "*What?! There must*

be some research that proves this lie true. Otherwise, doctors wouldn't keep repeating it, right?"

There are several kinds of skin cancer. The most dangerous and worrisome by far is melanoma. If sunlight exposure increases the risk of melanoma, it would be easy to prove with scientific studies showing that you are more likely to get skin cancer on your face or other areas of your skin that receive the most sun exposure. However, this has not been the case. Melanoma is often on areas of the skin that experience minimal sun exposure or no sun exposure at all. There is no research proving that melanoma is more likely to occur at sites of repeated sun exposure. This one fact alone should cause doctors to rethink their sun-blocking advice.

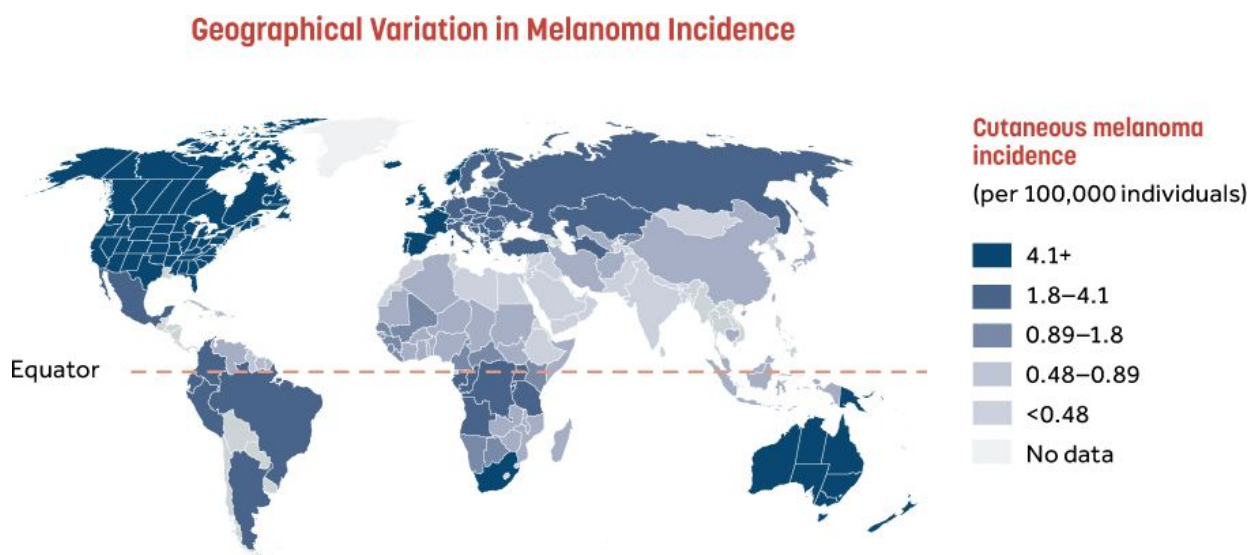
As we've started to use more sunscreen and wear more hats and long-sleeved shirts to block the sun, researchers should have been able to detect a decline in the rates of melanoma. However, the research shows that rates of melanoma have increased in the past decade.

Every research study cited by the AAD or the ASDS contains flaws in the method, number of participants in the study, or the conclusions drawn from the results. If another researcher attempted to use the same study design to prove that sunlight does *not* cause cancer, the AAD and the ASDS would have a field day discrediting that study because of its fatally flawed study design. Your doctor's job is to dig into research and prove to himself that the conclusions are valid before he gives you advice based on a study. Unfortunately, doctors seldom spend the time to make an effort to do this.

The sad truth of how things usually work in the real world is that a primary care doctor sees a news story on television reporting that the National Academy of Super Geniuses has decided that Something causes Another Thing, and Everyone should avoid that Something. With no research or real thought, this doctor then starts recommending to his patients that they avoid Something. This doctor might also skim the first couple of paragraphs of an article in a medical journal about this Something-causes-Another Thing topic. Based on his cursory inspection of the article, he still concludes that he should tell his patients to avoid that Something. Unfortunately, that doctor doesn't bother to read how the researchers conducted the study, the number of participants in the study, or if the conclusion matches the findings, which is all information he needs to make a good assessment about what his recommendation should be.

You might be surprised to learn that there's a sizable amount of research demonstrating that sunshine actually reduces certain kinds of skin cancer, as well as cancer in other parts of the body. One large study showed that people who work outside in the sun are less likely to get skin cancer than indoor workers. (Yes, you read that right.) Another large study shows that living further from the equator is a risk factor for skin cancer and other types of cancers. (Yes, you also read that correctly.) Because these studies don't support the popular expert opinion of the moment, they get little traction with doctors or the news media; therefore, you might have never heard of them.

Here's the important question we should all be asking: Why are we only researching putting chemicals on the skin and/or avoiding the sun to decrease skin cancer? For instance, why are we not researching whether it matters what our skin is made of? In other words, someone should research whether the things we eat and drink increase our risk of skin cancer. Could it be that eating quality natural foods would help you build better skin that is much less likely to become cancerous? If you look at a map that shows the geographical variation in melanoma incidence, you might be struck by two things, first, melanoma occurs much more frequently in locations with weaker sunlight, and secondly, it occurs much more frequently in areas of the world that tend to eat a standard Western diet of highly processed sugars, grains, and vegetable/seed oils.



I've had many patients tell me an interesting thing: They found that after they had decreased the amount of grains and vegetable oils in their

diets and had started eating more colorful berries and veggies, they could spend more time in the sun without burning. A few patients who experienced severe reactions to the sun in the past were happily surprised to find that they no longer had these reactions after they started eating an improved whole food diet. So, why are medical scientists not interested in investigating whether there are things in our diet that increase rates of skin cancer?

The sun hasn't changed at all in the past fifty years, as we will discuss shortly. The ozone layer has changed a little in the last fifty years, but the average human diet has changed almost completely in the past 50 years. That sounds like an important place for researchers to look, if you ask me.

THE TAKE-HOME

So what should we make of all this? How can we think about this problem in a way that honors our extensive experience as a species on this planet while balancing it with what doctors are currently telling us? We have been told that the increase in skin cancer over the past few decades is because the ozone layer is getting thinner, which means it lets in more ultraviolet (UV) light. However, there is a major problem with that theory.

If you start at the North Pole, where the sun's rays are very weak, and travel south toward to the equator, the UV exposure you would receive from the sun along the way would increase by more than 5,000 percent as you near the equator. People who live along the equator in places like Ecuador, Brazil, and Kenya, regardless of skin tone, receive many thousands of times the UV radiation as people who live in the far north in places such as Norway, Canada, and Russia. For the increased UV radiation that enters our atmosphere through a thinning ozone layer to be the cause of the skin cancer epidemic, wouldn't the UV levels need to be increased by an amount greater than the naturally occurring increase one would encounter while traveling from the far north toward the equator? Ozone depletion during the past fifty years has been reported by leading climate scientists to have increased UV exposure by, at most, 20 percent. This is a minuscule percentage compared to the large increase in UV exposure caused merely by traveling from Canada to Brazil. This fact alone should cause every doctor to reevaluate what he believes about this topic. The UV exposure from the sun because of ozone depletion has barely changed, yet we have a growing skin cancer epidemic. What else could possibly be to blame?

Your skin is made of what you eat. Your skin is completely replaced with new skin cells every month or two, and the new cells are made of the proteins, fats, and other nutrients you have eaten, for better or for worse. Therefore, what has changed over the past fifty years that could lead to these increasing rates of skin cancer? We've established that the sun hasn't really changed. And the ozone layer has changed a tiny amount, but not nearly enough to account for our skin cancer epidemic. How much have our food choices and food quality changed over the past fifty years? A heck of a lot.

During this past century, our species has gone from eating a mostly organic, vegetable-rich food supply grown by local farmers to eating a mass-produced, grain-heavy food supply that is grown, harvested, and processed by large corporations. Our diet is much higher in sugar, grains, and vegetable oils, not to mention questionable chemicals that are added, either accidentally or on purpose, during manufacturing. Why does no doctor ever stop to consider this as it relates to skin cancer?

The building blocks that our body receives for building our skin (and performing other functions) have changed. In the meantime, all doctors focus on telling patients to avoid the sun, to slather our skin with expensive protective products, and to have an expensive medical procedure to remove a piece of damaged skin. On the AAD's skin cancer prevention web page, there is no reference to how your diet might be related to your risk of skin cancer. This is a shame. Why is a website seemingly dedicated to skin health passing up on such a wonderful opportunity to educate people on how important a proper diet is in the prevention of skin cancer?



Are we doctors really so simpleminded that we need to think, “Because the sun shines on the skin, then skin cancer must be the sun’s fault”? If you built the roof of your house with shoddy materials, and it collapsed after a few years, did sun exposure on the roof cause the collapse, or were the building supplies you used to build the roof to blame? Part of the explanation for this seeming simplemindedness is how companies make money for *preventing* skin cancer, and how doctors are paid for treating skin cancer.

Companies are paid to develop products that block the sun. There are now hundreds of different kinds of sunscreens on the market. The more blockage they provide (the higher the SPF), the more they cost. If a company develops a sunscreen that is better, easier to use, cheaper to purchase, and so on, then the company's profits increase. A company would make very little profit at all by telling people to stop eating junk food. The same concept applies to how doctors are paid to treat and remove skin cancers.

Insurance pays a doctor about the same amount for a routine office visit as they pay to remove a noncancerous skin lesion. For removing a precancerous skin lesion (*actinic keratosis*), the doctor is paid roughly twice the amount that's paid for an office visit. Therefore, just by *calling* a skin lesion a precancerous lesion, a doctor can double what he is paid to remove it. If the lesion is diagnosed as cancer, with or without a pathologist confirming the diagnosis, the doctor is paid anywhere from four times the cost of an office visit fee up to many times more to remove that lesion.

If the doctor removes a large enough piece of skin, the patient also needs expensive skin grafting procedures to repair the defect, and, of course, that's another charge. You can easily see how it's in the doctor's financial best interest for your skin lesion to be labeled precancerous or skin cancer. The same doctor who makes the precancerous or skin cancer diagnosis would have been paid very little to counsel you years earlier to avoid eating grains or using vegetable oils in cooking and to include certain vitamins in your diet to prevent skin cancer from ever starting in the first place.

Before you gallantly jump to your doctor's defense and say that he would never stoop so low as to misdiagnose a skin lesion, consider this. The diagnosing of a skin lesion as something worse than it actually is has become so common that the practice has a name; an article in the *British Journal of Dermatology* calls this practice *diagnostic drift*. This article reveals diagnostic drift to be a significant cause of the skin cancer epidemic that we have been hearing about over the past few decades. If a doctor's prestige and income depend upon a skin lesion being cancer, then, more often than not, that lesion will be diagnosed as cancer. Refer to [Chapter 2](#) to understand why this is not necessarily caused by dishonesty or some kind of conspiracy. It is just human nature.

I know this chapter has given you a lot to think about and question. I'm also aware that dermatologists will not be thrilled with me for having spilled these particular beans. However, my duty is to my patients and to you, dear

reader. If I, as other doctors have done, ignore common sense and blame something as natural as the sun for this skin cancer epidemic, then I am a part of the problem. My plan, however, is to be part of the solution, come what may.

DO AS I DO

I eat many servings of colorful veggies every day, take my vitamins, and play in the sun all I want. I rarely use sunscreen. I have a fair complexion, so I still burn if I stay in the sun too long, and I try never to do that. Sunburns that cause peeling hurt, and that kind of extreme sun exposure might be what leads to an increased skin cancer risk.

When I ate a processed, grain-based, junk-food diet, I sunburned easily and terribly after only a short time in the sun. I probably had a much higher risk of skin cancer back then as well. Talk to your doctor about the real causes of skin cancer, and make sure to read and research. You can then decide how you and your family will work and play in the sun to keep your skin healthy.

HOMEWORK

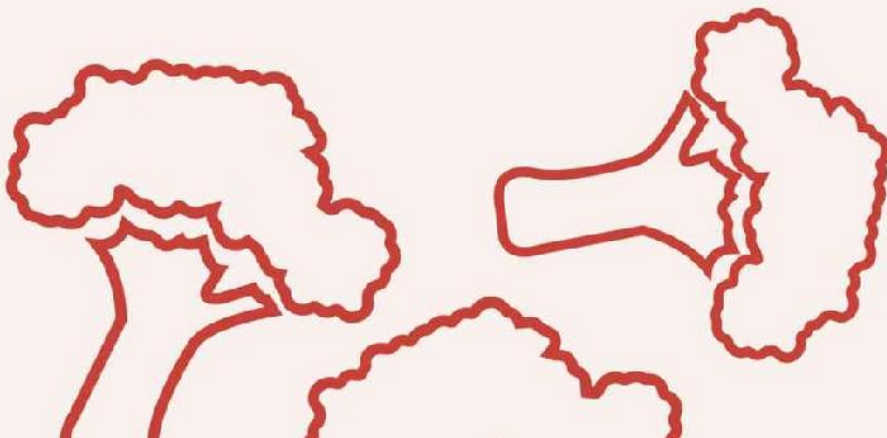
The homework for this chapter is more involved than what I've assigned in other chapters. I want you to email the AAD (www.aad.org/Forms/ContactUs/Default.aspx) and the ASDS (www.asds.net/Skin-Experts/Contact-ASDS) and ask to have copies of the research studies that prove that sun exposure leads to skin cancer. Ignore the BS, bluff, and bluster you will receive in reply and look only at the facts. You are likely to get a stack of brochures stating the societies' official opinions and positions, but you probably won't receive any actual research studies. Then, the next time you're at your doctor's office, ask him the same question. Tell him to take his time and find the most powerful study he can that shows the link between sun exposure and skin cancer and email a copy to you.

You will be amazed, and perhaps disappointed, at the dodging and subject-changing that takes place. Don't be tricked or dissuaded; be respectfully persistent. If you receive an email containing a study, read it carefully and research it. I think you will discover the actual findings in any

study sent to you will be lacking and lame and not worthy of making you
fear something as natural as sunlight.

Chapter 20

FIBER IS NECESSARY FOR A HEALTHY GUT



**No organ in the body is
so misunderstood,
so slandered and
maltreated as the colon.**

—Sir Arthur Hurst



THE LIE

Fiber is good for you, and you should try to get as much fiber in your diet as possible. Fiber will help with constipation and irritable bowel syndrome (IBS). Fiber will help prevent diverticulitis and probably even colon cancer.

WHY YOU SHOULD CARE

If fiber is vital for gut health then you should eat lots of it. However, if fiber is actually irritating to your gut, as several studies show, then you should probably limit your fiber intake, especially if you have IBS or diverticulosis.

SUPPORT FOR THE LIE

Everyone, from your parents to your doctor to your dietitian, is quick to tell you that fiber is good for you. The Big Food industry also loves repeating this lie because it's easy for them to add a little fiber to whatever junk they're trying to sell you, and they then put a "high-fiber" label on the box. People will tell you that getting extra fiber will prevent constipation, diverticulosis, and even colon cancer. There are several observational studies based on self-reported Food Frequency Questionnaire (FFQ) data that seem to support this hypothesis. The problem is, there are no randomized controlled trials (RCT) that show any of this to be true.

Although the observational studies seem to show a correlation between increased fiber intake and decreased rates of constipation, diverticulosis, and colon cancer, an observational study does not prove causation. The observational studies counted the dietary fiber from vegetables and fruit rather than from the fiber the food industry adds to junk food.



THE COMMON SENSE

Fiber is undigestible plant matter that passes through the digestive tract and is expelled unchanged in the feces. You can often see high-fiber foods in the toilet, unchanged in appearance from when you ate them. The Institute of Medicine currently recommends a daily fiber intake of 38 grams for men and 25 grams for women.

If you see a group of firefighters in the front yard of a house, it is highly likely that the house is burning. This does not mean the firefighters caused the fire; they are merely associated with the fire. The firefighters' presence in the yard proves correlation but not causation. In the same respect, the fact that eating more fibrous vegetables and fruits is correlated with decreased risks of colon/bowel problems does not prove that the fiber is preventing those conditions.

Most people who include many fiber-filled vegetables and fruit in their diet also eat diets that are healthier overall, and they live healthier lives. They are less likely to smoke, drink alcohol heavily, or eat lots of processed junk food. In many of the studies, these confounding variables are not controlled for, and thus may be the cause of the increased risk of colon/bowel disease rather than the lack of fiber.



For most of their existence on this planet, humans ate lots of fatty meat and a few vegetables. They certainly ate berries, fruits, and honey when they could get them, but this was rare. There is no evidence that our ancestors went out of their way to eat extra fiber.

THE RESEARCH

Virtually all the research suggesting that eating more fiber is good for you is in the form of prospective, observational studies, which don't prove causation. This is not sufficient evidence for a doctor or dietitian to tell patients to eat more fiber. When controlled studies are done on the topics of constipation, diverticulosis, and colon cancer, adding more fiber to the diet has no effect whatsoever on the outcome of the study.

One review article, which looked at multiple studies that investigated whether fiber played a role in the treatment of chronic constipation, found that the less fiber the participants ate, the fewer symptoms of constipation they had. You read that correctly. The participants who ate the most fiber had more severe constipation symptoms than those in the study who ate no fiber at all.

Two large studies seemed to show no colon health benefits from eating more dietary fiber. The Nurses Health Study followed 88,757 women for years and found no increased risk of colon cancer in the women who ate the least fiber. The Health Professionals Follow-Up Study followed 47,949 men for years and also found no difference in colon cancer rates between the men who ate the most fiber versus those who ate the least fiber.

THE TAKE-HOME

As with all dietary topics, we should look to our past to understand what we should eat in the present. Although it is known that our ancestors would

travel great distances to acquire certain nutrients (such as salt), there is no evidence that our ancestors went out of their way to get extra fiber. Fiber is an indigestible irritant to our bowels, and it can act as an antinutrient, preventing absorption of some vitamins and minerals we need. If I told you to eat a cup of sawdust (full of fiber) each day in order to keep your bowels healthy, cancer-free, and moving regularly, you might think I was crazy. But, the fiber many experts recommend that we eat actually contains sawdust (or wood fibers that are very much like sawdust). This recommendation does not square with how our ancestors ate. Until some good, controlled research proves the advice to eat more fiber to be correct, experts should stop advising their patients to do so.

There are people, and other animals, who eat a Carnivore diet (all meat—no plant matter at all—and zero grams of fiber) for years at a time. These people report no constipation and no increased risk of diverticulosis or colon cancer.



Any fiber you eat should come from whole, unprocessed vegetables and never from factory-added fiber that's in junk food. Any possible good you would get from eating added fiber (from sawdust or grains) is offset by the inflammatory properties those additives would produce. The worst possible source of fiber is a bowl of highly processed grain cereal with added pseudofiber.

DO AS I DO

I never go out of my way to eat extra fiber. In fact, there are many days each week when I eat no fiber at all. I believe humans have eaten mostly fatty meat for thousands of years, and I try to mimic this way of eating. I

occasionally eat some vegetables, but what I eat seldom contains more than a few grams of fiber.

Even though I eat very little fiber, if any, each day, I have no problems in the restroom, no pain, no cramping. It might be that some people need some small amount of fiber in their diet to prevent constipation issues, but I am not one of them.

HOMEWORK

This lie has reached such mythological proportions that it will likely take years for the average person to begin to understand the truth about added fiber. Big Food makes billions of dollars from highly processed added-fiber foods, so the manufacturers will certainly be pumping the brakes of paradigm shift as often as they can. Here are a couple of resources to help you start to make sense of this topic.

Blog Post: “*A Carnivorous Diet*” by Amber O’Hearn on the Empirica website (2012) at <http://bit.ly/NoFiber>

Long-time carnivore Amber O’Hearn breaks down the science and practical results of a fiber-free diet.

Paper: “*Myths and Misconceptions About Chronic Constipation*” by Stefan A. Müller-Lissner (2005) at <http://bit.ly/ChronicConstipation>

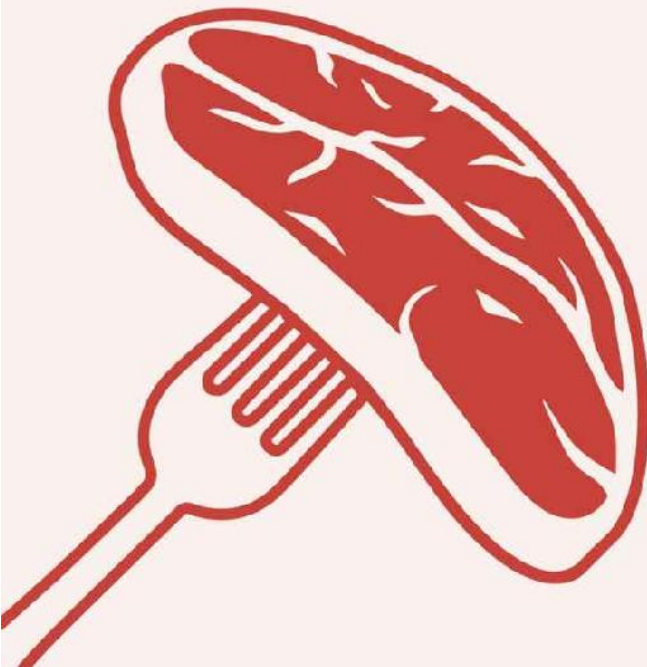
The article discusses classic myths (lies) about what does and does not cause constipation.

Blog Post: *World Carnivore Tribe* at <http://bit.ly/CarnivoreTribe>

This Facebook group has more than 25,000 members at this time. Here you can read the stories of thousands of happy people who have been fiber-free for years, and you can ask them your questions.

Chapter 21

EATING RED MEAT CAUSES CANCER



**The soul becomes dyed
with the color of its
thoughts.**

—Marcus Aurelius



THE LIE

Red meat is not good for you, and eating more than a single small serving daily will increase your risk of colon cancer or increase your cancer risk overall.

WHY YOU SHOULD CARE

If eating red meat increases your risk of developing cancer, then you should avoid it. However, if red meat does not cause cancer, you should eat lots of red meat to take advantage of all the nutrition it contains. There is no question that red meat is filled with vitamins, minerals, protein, and healthy fats.

SUPPORT FOR THE LIE

The World Health Organization (WHO) has proclaimed red meat to be a probable cause of cancer in humans. Due to this risk, the WHO advises that humans limit red meat in their diets. The recommendation is based on a few prospective observational studies that showed a slight correlation between eating red meat and increased risk of cancer. The data for these studies came from self-reported data collected on Food Frequency Questionnaires (FFQs).

All the experts on this subject bluster and blow about the absolute truth of this lie, but the actual research is quite anemic. Not a single controlled study proves any link between eating red meat and increased cancer risk.

THE COMMON SENSE

Humans, in our present form, have been eating red meat for at least 200,000 years. Long before we cultivated grain, fermented wine, or made cheese, we were hunting large animals and eating their meat. Our ancestors hunted many species of large animals to extinction. To now say that the red meat that has nourished us for millennia has become bad for us seems silly from a commonsense standpoint.

Our species flourished and prospered by eating the meat of large mammals. Indeed, some experts believe the reason our brain size increased to its current size is because of the quantities of fatty red meat our ancestors consumed. So, if science is going to tell us that a food that has nourished us

for so long is now bad for us, there'd better be some hard data to back up that claim.

THE RESEARCH

As with other lies I've discussed, the research to support the lie that red meat is a probable cause of cancer comes from poorly conducted epidemiological studies, which show correlation between two things rather than proving that one thing causes the other. Most of these observational studies are based on those food frequency questionnaires that contain self-reported data from the research participants. Questions such as, "How many cups of ribs have you consumed in the past 3 months?" are difficult to answer, and participants are likely to guess or estimate to come up with a response.

Another problem with this kind of research is the researcher's preconceived ideas. Because this type of study is neither randomized nor double-blinded, the preconceived notions of the researcher can seep into the results of the study, and very often do. This bias is not evidence of dishonesty; it's just human nature to see what you are expecting to find.

Fear of judgment can keep study participants from telling the complete truth. If the respondents think someone is going to be reading the results making judgments about the answers, they might very well fudge on their answers one way or another. Researchers are unable to control for this reaction from participants, so the FFQs typically yield little useful information.

Confounders are other things that could be leading to the outcome the study is looking for. For example, many people who eat lots of red meat also smoke and drink alcohol, both of which increase cancer risk. If these types of variables are not controlled for in the study, they can skew the results and give false conclusions. Many studies that seem to show a link between red meat and cancer did not control for smoking, alcohol intake, or activity level. Not adjusting the data for such confounders renders the results of the study useless.

It's true that the link between smoking and lung cancer was deduced from epidemiological studies, but smokers showed a 15 to 30 times greater risk of lung cancer than nonsmokers. Although the results didn't prove that smoking causes cancer, the high relative risk makes it very likely to be a cause. In the case of the epidemiological research linking red meat to cancer

risk, the results showed barely 1.5 times greater risk. Most researchers don't even pay attention to relative risks lower than 2, and the red meat-to-cancer link just doesn't make the cut.

THE TAKE-HOME

Given the very long history of humanity eating all the red meat it could hunt down and kill (we drove several large species to extinction), it seems unlikely that eating red meat leads to anything other than good health. If red meat truly causes cancer, then it seems possible that humans should already be extinct because of all the cancer our ancestors would have had from eating all that red meat. There is no evidence in anthropology or archeology that our ancestors considered red meat to be anything other than a delicious, healthy food.

When we stop depending on newspaper headlines for our scientific knowledge on this topic and actually dig down into the research, we come away with very little evidence that red meat causes cancer. Researchers who truly believe this should design some better studies that will show a convincing link between red meat and cancer.

DO AS I DO

Red meat is a large part of my daily keto-carnivore diet. I eat red meat grilled, smoked, fried, and roasted. I have no fear that red meat will make me anything other than very healthy, just like it did for my ancestors. Red meat cooked over an open flame nourished my ancestors for thousands of centuries, and it nourishes me as well. I keep an eye on the research, but so far I've seen nothing that makes me fear enjoying the nutrition in red meat.

HOMEWORK

There are groups who would prefer you eat a plant-based diet and not eat animal-sourced foods. They include the vegan-vegetarian groups, Big Food, and Big Pharma. The vegan/vegetarian groups believe it is morally wrong for humans to eat other animals, even though we've done so for millennia. Big Food makes millions of dollars through manufacturing processed plant-based food products, so their motivation is clear. Big Pharma, as is often

usual, is currently so confused and misguided about this topic that its motivation is unclear.

BOOK: *Eat Meat and Stop Jogging: “Common” Advice on How to Get Fit Is Keeping You Fat and Making You Sick* by Mike Sheridan (2014)

This book is about the benefits of eating a meat-heavy diet. And it suggests you stop jogging if you hate it, like I do.



Chapter 22

YOU MUST EAT LOTS OF CARBOHYDRATES TO FUEL YOUR BRAIN



**Whenever a doctor cannot
do good, he must be kept
from doing harm.**

—Hippocrates



THE LIE

You must eat plenty of carbohydrates each day, or your brain and other body parts will not have enough energy to function properly.

WHY YOU SHOULD CARE

If eating carbohydrates is essential to proper brain and body function, then you should eat lots of carbohydrates at each meal. However, if you don't need carbohydrates to power the brain and other organs, and they lead to increased levels of blood glucose and insulin, then you should limit them.

SUPPORT FOR THE LIE

It seems most doctors and dietitians will repeat this lie effortlessly. It most often comes out of a doctor's mouth when a patient asks about doing a low-carb diet for weight loss. The doctor issues a stern warning: "Your brain can't function properly unless you eat some number of carbohydrates three times daily, with more carbohydrate snacks in between." Big Food is happy to support and repeat this lie because the carbohydrates found in sugar and grains provide cheap ingredients that manufacturers can use to make all manner of tasty snacks.

It's obvious why Big Food is happy to repeat this lie, and most dietitians were trained in schools of nutrition founded and funded by Big Food. But why are doctors so quick to repeat it? We are taught the biochemistry of carbohydrate metabolism. We are taught that glucose (the sugar your body uses for energy) can be made from carbohydrates, proteins, and fats that we have eaten. Unfortunately, somewhere along the way doctors forget this training and buy in to the lie that humans must eat carbohydrates to function.



THE COMMON SENSE

There have been societies in which individuals lived their entire lives while eating a zero-carbohydrate diet for months at a time. These societies were well known to the scientific community in the past, and they should be well known to medical science as well. It seems that their good health and perfect dentition has currently been forgotten by both the scientific and medical communities.

For example, the Inuit tribes of the arctic regions of Alaska, Canada, and Greenland lived in a part of the world where few plants could grow. The majority of their diets (more than 90 percent by some estimates) was the fatty meat of whales, walrus, caribou, seal, and polar bears. It was so cold where they lived that it was impossible to grow plants. They would eat small amounts of berries, roots, and tubers during certain months of the year, but, on the whole, they ate very few, if any, carbohydrates for months at a time. Obviously, if the brain needed a certain amount of carbohydrates each day to function, the Inuit would have been extinct centuries ago. But they are still with us today despite the almost zero-carb diet, which was recorded by anthropologist Vilhjalmur Stefansson.

Stefansson lived among the Inuit for several years in the early twentieth century, and he was so impressed with the overall health of the people that he adopted their fatty-meat diet. When he returned to the United States and told of his dietary discovery, he was ridiculed and labeled as dishonest. To prove what he had witnessed, he agreed to be monitored for a full year of eating only meat. The skeptics watched closely as Stefansson flourished on his meat-only diet. He didn't develop any deficiencies, and he remained perfectly healthy.

Another community that flourished on a carnivore diet was the Masai people of Eastern Africa. The Masai diet was raw meat, raw milk, and raw blood from cattle. The tribe's dietary habits were studied closely by Dr. Weston A. Price, who reported that despite their zero-carbohydrate animal diet, they were very healthy and strong. Multiple other societies lived on meat almost exclusively, including the Cukotka in Russia, the Samburu and Rendille warriors of Africa, certain nomad tribes in Mongolia, the Sioux of South Dakota, and the gauchos from Brazil.

Today there are thousands of people who live very happily on zero-carb or very low-carb diets. They report being very healthy and energetic

despite going for months at a time with no carbohydrates at all. There is no anthropological or physiological evidence that humans need to eat a certain amount of carbohydrates daily.

Some cells in the human body need glucose for energy. The red blood cells do not have a nucleus, or their own mitochondria, and thus they have no means of producing their own energy or burning fat as fuel. Certain cells in the brain and eye also need glucose for energy. However, your liver is perfectly capable of making all the glucose your body needs through a process called *gluconeogenesis*. Because the liver can produce as much glucose as these cells need to function perfectly, there is no need to eat carbohydrates.

THE RESEARCH

There is no meaningful research showing any need for daily carbohydrate intake in human beings. Although there are many “experts” who say otherwise, they don’t have research to back up their claims. The liver can convert both amino acids and fatty acids into glucose for the cells that require glucose for fuel; you don’t need to eat carbs.

THE TAKE-HOME

Many generations of humans have lived in situations where they had no access to carbohydrates for months at a time. Whether humans at one time did need carbohydrates and became genetically adapted to live without them or never needed them to start with is unknown, but at present you don’t need to meet a minimum daily requirement for carbohydrates.

Most of the cells in your body can shift from needing carbohydrates as fuel to being able to burn some form of fat as fuel. Every human body has the biochemical machinery to make this shift from being a carbohydrate-burner to being a fat-burner; it just takes a little time to make the conversion. In no way does this limit your metabolic flexibility. Your body is always capable of burning carbs as fuel in the future, if you’d ever want that to happen.

For the few cells in your body that cannot use fat for fuel, your liver is happy to use gluconeogenesis to produce enough glucose to feed the cells

just what they need. This process exists for a reason, and it clicks on without any effort on your part.

DO AS I DO

I often go days without eating anything but fatty meat cooked in either lard or butter. Some cuts of meat have 1 or 2 grams of carbohydrates, but that's not nearly the amount we are told we need to fuel our brains. I eat a little green veg now and then, but I do it more for taste than for the carbs. I have been low-carb or zero-carb for so long that my brain has adapted very well to burning fat as fuel, and my liver makes all the glucose my body needs for other functions on a moment's notice. Your body can do this, too.

HOMEWORK

Even though your doctor or dietitian might tell you your brain needs lots of carbs to function well, millions of people are doing great on a ketogenic diet. Here are two great resources to help you understand just what the body needs and what it does not.

Book: *Real Food Keto: Applying Nutritional Therapy to Your Low-Carb, High-Fat Diet* by Jimmy Moore and Christine Moore, NTP (2018)

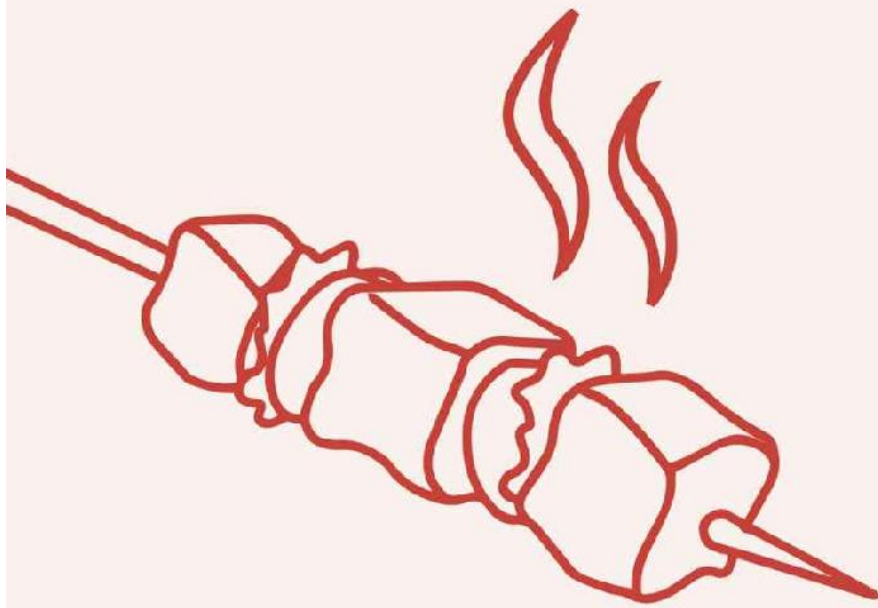
This excellent resource helps you formulate an ancestrally appropriate ketogenic way of eating.

Book: *Eat Rich, Live Long: Mastering the Low-Carb and Keto Spectrum for Weight Loss and Longevity* by Ivor Cummins and Jeffry Gerber, MD (2018)

Learn about the root causes of chronic disease and the diet that will prevent you from having them.

Chapter 23

GRILLING MEAT CAUSES CANCER



**But it appears common,
and has been found all
over the world in all ages,
that meat is considered
the superior food,
vegetables inferior or
secondary.**

—Vilhjalmur Stefansson



THE LIE

Eating charred meat cooked over an open flame will increase your risk of colon cancer or increase your risk of cancer overall.

WHY YOU SHOULD CARE

If grilling meat increases your risk of cancer then you should prepare the meat using another cooking method at a lower temperature. However, if grilling meat, as humans have done for thousands of years, does not increase your risk of cancer, then you can enjoy grilled meat without worry.

SUPPORT FOR THE LIE

This is another lie that has been virtually created by the World Health Organization (WHO) in one of their publications. There are several epidemiological observational studies that show a very weak correlation between grilled meat and risk for cancer. There are also a few rodent studies, most of which are poorly designed, that seem to show an increased risk of cancer in the rodent when it had been eating charred meat. However, the rodents in the studies consumed the supposed cancer-causing compounds at a level hundreds of times the amount the average human would eat.

There have been no randomized, controlled trials in humans that support this lie as being truth. Also, there are multiple observational studies that don't show any correlation between grilling meat and cancer risk. When you search for literature on this subject, it becomes obvious that there is much bias in the research, and the researchers have let emotional belief influence the conclusions of the study. Without blinding and/or randomization in their studies, this emotional bias seeps into the findings and undermines the research as reported.

THE COMMON SENSE

There is evidence that humans and our immediate predecessors have cooked meat over an open flame for hundreds of thousands of years, if not much longer. If there was any meaningful cancer risk from doing this, humans would either be extinct, or we would have stopped cooking meat by this method thousands of years ago. The trial-and-error of life tends to make an animal stop a certain behavior and pick up another behavior if there is a

benefit in doing so. At some point in our history, we most certainly would have stopped grilling meat over an open flame if it yielded a cancer-causing meal.

The researchers on the WHO side of this argument are very emotionally invested in their viewpoint because they believe that a plant-based diet is best for humans and for the planet. Being so emotionally involved in such a research question makes the proponents of the grilled-meat-causes-cancer hypothesis very ardent and convincing. They are quick to promote their hypothesis as fact, even though it is barely a hypothesis. To the average observer, a passionate researcher seems very believable. However, being passionate and emotional about a topic does not make you correct.

THE RESEARCH

The WHO has proclaimed that certain compounds in grilled meat lead directly to cancer. They have based this opinion on the results of epidemiological observational research studies that seem to show a correlation between these compounds and cancer of various forms. Remember, though, that this type of research can show a correlation, but it can never *prove causation*. The studies show only the slightest correlation between eating grilled meat and cancer risk, and the relative risk is very low—almost nonexistent. The same style of studies were used to show the link between smoking and lung cancer, but with a big difference.

The studies on smoking and cancer showed a very high correlation with a very high relative risk. This means it is very, very likely that smoking increases lung cancer risk, even though the research doesn't prove the causation. The participants in the study had no other confounder in common that could explain the increased cancer incidence in the smokers.

The questionable compounds in grilled meat are acrylamides (ACs), heterocyclic amines (HCAs), and polycyclic aromatic hydrocarbons (PAHs). In rodent studies, these compounds from the grilled meat were highly correlated with cancer in mice and rats, but the quantities of the compounds were thousands of times the amount a human would ever eat. One problem with using the rodent studies to draw conclusions for humans is that humans have grilled meat over an open flame for hundreds of thousands of years, whereas rodents have not. Another issue is that rodents have a different diet than humans and a very different digestive system. There have been no randomized, controlled trials in humans, and there aren't even any

observational studies that come close to showing a strong correlation, or causation, between eating grilled meats in normal amounts and increased cancer risk.

THE TAKE-HOME

Rats and mice in the wild eat berries, bugs, grain, and sometimes raw meat. They never eat grilled meat, and they never have. To feed them high levels of compounds produced by grilled meats is sure to upset their system because it is not their ancestral food. In the studies to determine a relationship between grilled meat and cancer, the rodents ate levels of these compounds thousands of times higher than even the most fervent human carnivore would eat. This obviously doesn't prove much.

Since before recorded history, humans have been grilling fresh meat over an open flame. It is part of our ancestral diet as far back as archeology and anthropology can track. If you've ever tried to cook fresh meat over an open flame, even with the most modern grilling equipment, you know the impossibility of not charring at least some of the meat. Thus, it defies common sense to claim that humans should be afraid of grilled meats, even when they eat grilled meats on a daily basis.

Two of the compounds in grilled meat that we're supposed to be afraid of, HCAs and PAHs, do cause increased incidence of cancer when consumed at thousands of times the normal levels. But that's the key information: *thousands of times the normal levels*. So, in other words, you shouldn't eat more than one hundred grilled rib-eye steaks daily. Obviously, though, that's way beyond what anyone is going to consume. Also, would it surprise you to hear that these compounds occur in many other foods the WHO considers very safe for you to eat? Well, they do.

ACs appear in some foods naturally, and they're in any fried food and any food that has been browned. French fries, toast, prune juice, breakfast cereals, roasted nuts, coffee, cocoa, potato chips, and cookies are examples of foods in which we can find ACs. When you toast bread until it is even a little brown, you create acrylamides, and those acrylamides are added to the acrylamides produced in the bread when it was baked.

Cooking vegetables causes high levels of a compound called benzopyrene, which is thought to increase cancer risk. (Why this is not talked about more is a subject for another day.) Any food that contains amino acids—the building blocks of protein, creatine, and sugar—can

produce HCAs and PAHs. This includes any bread, veggies, and potatoes that have any meat juice on them at all. We know these vegetable-source foods contain proteins, because our vegan friends tell us so, and they definitely contain sugars because that is what carbohydrates are made from. If these plant foods come into contact with meat during their cooking, then they can produce HCAs and PAHs. To avoid HCAs and PAHs, you would have to eat all of your food in its raw form—no cooking allowed. Obviously, this is not what humans have been doing for thousands of years. We have been cooking at least some of our food since fire was harnessed as a tool, and it's very common to cook meat and plant foods together.

DO AS I DO

I have no fear of grilled meat. I eat it as often as I can, and I feed it to my family as often as I can. The research on this subject is trivial at best, and it's filled with researcher bias. Until meaningful research is produced that shows that the way our ancestors prepared their food is now dangerous, I will continue to enjoy it.

HOMEWORK

Grilling meat over an open flame is just about as human as you can get. Despite the many resources that perpetuate the myth and misconceptions, there are some reliable sources of information out there. Here is a great one.

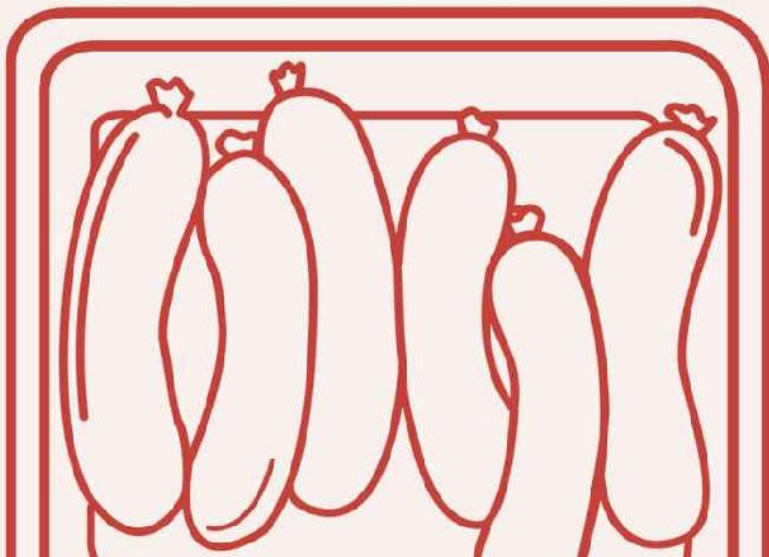
Book: *The Big Fat Surprise: Why Butter, Meat & Cheese Belong in a Healthy Diet* by Nina Teicholz (2014)

Teicholz destroys the silly arguments that meat is somehow unnatural and unhealthy for you.



Chapter 24

**EATING
PROCESSED
MEAT
CAUSES
CANCER**



**Beware of false
knowledge; it is
more dangerous than
ignorance.**

—George Bernard Shaw



THE LIE

Processed meats, such as bacon, sausage, bologna, and hot dogs, contain high levels of nitrates and nitrites which will cause you to have cancer.

WHY YOU SHOULD CARE

If processed meats are full of nitrates and nitrites, and these nitrates and nitrites increase your risk of cancer, then you should limit or avoid them. However, if processed meats contain fewer nitrates and nitrites than many vegetables, and these compounds have not been definitively shown to increase cancer risk, then you can enjoy processed meats as part of a healthy, affordable diet.

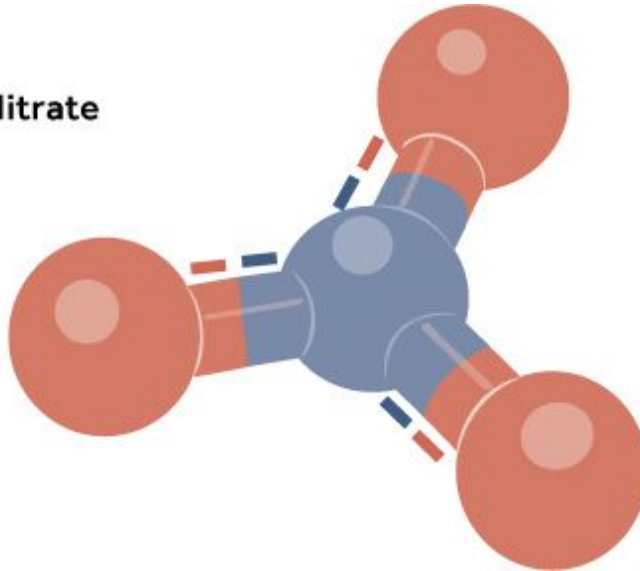
SUPPORT FOR THE LIE

The International Agency for Research on Cancer (IARC), an organization working under the World Health Organization (WHO), announced that processed meats were a probable cause of cancer. The group formed this opinion based on research from animal (rodent) studies, observational studies, and population studies. IARC claimed to have 800 studies showing the connection between processed meats and cancer, but fewer than five of these studies are published. These epidemiological studies show a very weak correlation between eating processed meats and increased cancer risk. At the time I'm writing, there have been no controlled trials that prove this hypothesis.

Nutritionists, dietitians, and many other experts accept as fact that processed meats are a cancer risk. The official consensus is that processed meat is dangerous, and we should avoid it. It is considered unacceptable, almost taboo, for a doctor or other health/nutrition professional to question this belief.

THE COMMON SENSE

Nitrate



Nitrates are chemical ions containing a nitrogen atom and three oxygen atoms arranged as in the illustration above. Nitrates can occur naturally in soil, can be made by bacteria, or can be synthetically made. Nitrates occur at very high concentrations in celery and beets. Nitrates are currently being researched for their medicinal purposes, as they improve blood pressure and reduce the risk of heart attack.

Nitrite



Nitrites are chemical ions containing a nitrogen atom and two oxygen atoms arranged as in the illustration above. Nitrites occur naturally, can be made by bacteria, can be synthetically made, and are produced in human saliva at hundreds of times the concentration found in cured meats. Nitrites also can be formed by chemically converting the nitrates found in celery and beets.

Processed meats do indeed contain nitrates and nitrites. The U.S. Department of Agriculture has set very strict guidelines on the amounts of nitrates and nitrites that can be in processed meats: Less than 500 parts per million can be used in the production process, and often only 10 parts per

million remain in the finished product. This amount might seem worrisome until you hear how much nitrate and nitrite are in many other foods and in your saliva.

For example, many vegetables contain much higher levels of these ions than processed meat. Celery and beet greens contain hundreds of times more than the average hot dog. Somehow, those groups that warn us of the dangers of processed meats overlook this fact. Imagine if experts told us to avoid vegetables because of their water content but said it's perfectly safe for us to drink a glass of water. This makes no sense, and neither does the nitrate/nitrite scare.

More than 90 percent of the nitrates the average person consumes comes from vegetables. Yes, you read that right. Celery, beet greens, and arugula contain more nitrates than one hundred hot dogs! If we are worried about nitrates, and the compounds they produce, then we should strictly limit veggies rather than processed meat.

Here's some information you might find surprising: The bacon and hot dogs that say "uncured," "organic," and "nitrate-free" contain more nitrates than the cheaper processed meat and hot dogs. Apparently we're supposed to consider the nitrates in organic and nitrate-free meats to be different because they come from celery and beet juice. A loophole in U.S. federal guidelines makes it permissible to ignore this nitrate (which is the exact same molecule as the one used in cheaper processed meat). So if a company uses celery juice as the source of nitrates, it gets to call the meat product "nitrate-free," even though the final nitrate amount is much higher than in other products.



Would you be surprised to hear that more than 90 percent of the nitrites you swallow each day do not come from food at all but from your saliva? Well, it's true, and it really puts the final nail in this myth's coffin. Your body naturally produces hundreds of times more nitrites in your saliva each

day than you could possibly get if you ate nothing but processed meat all day. Should we outlaw your spit as a possible carcinogen?

Hopefully, you're getting a sense of how foolish it is to be afraid of the small amount of nitrates and nitrites left in processed meats. If you truly fear nitrates then you should stop eating green vegetables. And if you fear nitrites then you should stop swallowing your own saliva.

THE RESEARCH

The research supporting this lie is laughable. When the paper from M.I.T. that started this scare was first published, the news media picked it up and ran with it. Lots of people heard the news. However, when the paper was later discredited and retracted, you barely heard a peep.

People who frequently eat processed meat tend to be less affluent than those who do not. They also tend to smoke more, exercise less, and do other unhealthy things. When researchers who performed the observational studies that show a correlation between processed meat and cancer risk were collecting their data, they used those untrustworthy Food Frequency Questionnaires (FFQs), and they did not take these confounding variables into account. They did not control for these other unhealthy behaviors, so the research is tainted. If someone who eats lots of hot dogs also smokes, drinks lots of beer, and never gets off the couch, are we surprised that their rate of having cancer is higher than someone who avoids hot dogs, doesn't smoke, works out, and drinks only rarely? I'm not. Were the hot dogs to blame? Almost certainly not. This obvious defect in the research is ignored by most experts who try to give us advice about the dangers of processed meat.

THE TAKE-HOME

This lie is another great example of a situation in which researcher bias and personal beliefs have been ensconced in nutrition dogma. When you look at the research with a critical eye, the lie completely falls apart. When you discover that "uncured" meat contains more nitrates than inexpensive processed meat, the situation becomes embarrassing. When you understand that your own saliva is by far the greatest source of nitrites in your body, the myth becomes completely laughable.

DO AS I DO

I enjoy processed meat as often as I like. I regularly feed my children hot dogs, bologna, and bacon. I have no fear whatsoever of the nitrates and nitrites in processed meats. I have, however, banned my family from eating vegetables and swallowing their own saliva. No, no—just kidding. But you get my point.

HOMEWORK

The following articles provide additional information about the nitrate and nitrite myth.

Web Article: “*The Nitrate and Nitrite Myth: Another Reason Not to Fear Bacon*” by Chris Kresser at <http://bit.ly/DontFearBacon>

Chris Kresser destroys the nitrate/nitrite myth and offers multiple references for more information in this great blog post.

Web Article: “*Does Banning Hotdogs and Bacon Make Sense?*” by Sandy Szwarc, BSN, RN, CCP, at <http://bit.ly/BaconIsGood>

Sandy explains the silliness of worrying about the nitrites in processed meat if you ignore the nitrites in veggies, and she provides lots of great references you can research yourself.



Chapter 25

LITTLE WHITE LIES



**Be careful about reading
health books. You may die
of a misprint.**

—attributed to Mark Twain



Various little white medical lies, like the ones in this chapter, are almost too numerous to count. I've included the most common ones here, along with a brief response to each. It's usually a relative or friend who tells you these lies, but there are still some doctors who also repeat them. If you hear one of these lies from your doctor, try to determine if he's joking. If he isn't, then run—don't walk—from his office in search of another source of medical care. Any doctor worth his co-pay should know better than to repeat any of these little white medical lies.

I've included these mostly for fun but also so you can tell the source of the lie that he or she is wrong. I'm a bit of a stickler over such things. We're supposed to be an intellectual, technologically advanced species. That should mean we don't believe silly things that aren't true. We should believe and repeat only things that are supported by evidence.

With that being said, here are some lies you can dispel for your friends and relatives.

We use only 10 percent of our brains.

MR (magnetic resonance) and PET (positron emission tomography) scans repeatedly have shown this statement to be false. To give this lie credibility, some people attribute it to Albert Einstein. All of your brain is working all the time—which is either a good thing or a bad thing, depending on how you use it.

You should drink at least eight glasses of water a day. Or more!

This lie likely comes from a recommendation the Nutrition Council made in the 1940s. That group recommended we ingest 64 ounces of fluids each day, but that recommendation was intended to include the water in the food we eat and in beverages other than water. No research has ever shown that you need a certain amount of clear water each day for health or weight loss. However, it's probably a good idea for you to drink a few glasses of good water every day. Your thirst mechanism is hard-wired, and it's very good at telling you how much fluid you need each day. It doesn't need your help in deciding how much water you should drink.



Shaved or cut hair grows back thicker and darker.

This lie has been disproved many times. I know; I know; it sure seems like the hair grows back darker and thicker, but it doesn't. I once argued with a cosmetologist about this lie and almost ended up exchanging blows over the topic. She assured me that this lie was definitely true, and her cosmetology textbook verified the statement. She said she would show me. Alas, after diligently searching for this lie in her book, without success, she decided to settle for throwing the book at me.

Reading in dim light (or watching TV too closely) is bad for your eyes.

Absolutely no research supports this lie. The human eye is one of the most impressive things in the known universe. Its ability to adjust to different situations is astounding. This lie was probably thought up by siblings who hated reading and wanted to mess with you. Or by your parent, who just wanted you to go outside to play.

Eating turkey will make you drowsy.

Turkey contains tryptophan, which is known to make you drowsy. The only problem with this little lie is that chicken, beef, and many other foods also contain as much (or more) tryptophan as turkey. What makes you drowsy (and fat) after a huge holiday meal are the starches and sugars, not the turkey.



Don't let someone who's suffered a head injury fall asleep.

If your friend has been knocked out due to head trauma, a doctor should evaluate him. After he has been checked, your friend is perfectly safe to take a nap if he wants, even if he has a concussion. If a doctor tells you not to let your friend go to sleep after suffering a head injury, I want you to roll your eyes as far back in your head as possible, snap a selfie of you and that doctor, and send it to me. I might include it in my next book. Falling asleep presents no danger whatsoever to someone who has sustained a head injury. Indeed, doctors sometimes induce a coma in a patient with a severe head injury, causing them to sleep for days.



Swallowed chewing gum stays in your stomach or intestines for years.

Umm, no. I'm not sure when or where this lie started, but it has no basis in reality. The ingredients of chewing gum (a detailed list is quite hard to come by) are probably unhealthy, but gum can pass through the gut at the same speed as all the other foods you eat.

You should wait an hour after eating before you swim.

No research supports this lie. I used to enjoy making friends and relatives nervous at picnics with this one. I would eat a huge plate (or two) of food, announce immediately afterward that I was going for a swim, and then dive headfirst into the nearest body of water. The fact that I didn't cramp and die seemed to have no effect on the continued belief in this lie by my friends and family.

Fingernails and hair continue to grow after you die.

Not true. After a person dies, their skin dries out and contracts because they are no longer drinking their eight glasses of water per day. The skin pulls away from the nails, thus making the nails *appear* to grow. Dead things do not grow.

Spicy foods cause reflux, ulcers, or other stomach problems.

Some foods do inflame your stomach and intestines, but it's not the spicy foods you should worry about. Some spices can burn or tingle your tongue, but they don't affect your stomach or intestines. Your stomach constantly deals with concentrated hydrochloric acid and laughs at these wrongly accused spices. The more likely causes of stomach irritation are stress, medications, sugar, dairy, and grains. If your doctor suggests that you avoid spicy foods, again, roll your eyes *waaay* back and take a selfie for me to put on the cover of my next book.



A woman can't get pregnant during her period.

Don't trust this one! Sperm can live in a woman's body for up to a week, and, as any woman can tell you, periods can be long or short, or even absent. It's unlikely that a woman will get pregnant from having sex during her true period, but it is definitely not 100 percent fail-safe.

You lose most of your body heat through your head.

According to research, probably done by scientists who were tired of being told by their moms to wear a hat when they go outside, you only lose 7 to 10 percent of your body heat through your head when you're outdoors in cold weather. Therefore, wear a hat if you want to, but it's optional. Feel free to

tell your mom about this lie, but you should still wear your hat when you go out if she tells you to.



Suicide attempts increase over the holiday season.

Research shows that the suicide rate is lower during December than in other months. I am not sure how this lie got started. It was most likely started because it makes a good story. We are always eager to believe that there's a cause-and-effect relationship between things like the time of year or phase of the moon and some other unrelated occurrence. (See the myth related to the full moon later in this chapter.)

Poinsettias are deadly.

No confirmed human or animal death has occurred from eating poinsettias. Out of the thousands of episodes recorded by Poison Control of people or pets eating poinsettia, the worst symptoms ever reported were vomiting and stomach cramping, just as you experience when you eat any other nonedible plant. Poinsettias are not edible, and they don't taste good (yes, I tried a little piece while researching this book), but if you're thinking of poisoning your annoying uncle this Christmas season, the poinsettia is not the plant you will want to use.

Eating at night makes you fat.

The time of day you eat, according to the research, has nothing to do with weight gain. It's all about *what* you eat rather than when you eat it. No research supports this lie about eating at night—not even a little bit. Eat at whatever time of day you want; just make sure to eat the right foods.

Emergency room and labor and delivery visits increase during a full moon.

I realize I will offend many nurses (including my wife, a labor and delivery nurse) by saying that this lie has been studied and found to be false.



It's not even a little true. I discovered that this was a lie when I was an emergency room doctor and was planning to do a study about this relationship. At the time, I believed this statement to be true. I began to study and obtain data, but the numbers I collected from three different small-hospital emergency rooms weren't showing any relationship between trauma and the phase of the moon. After a little more research, I found out that the Mayo Clinic had already conducted a large study proving the phase of the moon was irrelevant to ER visits, and I abandoned my study. Sorry, nurses; please forgive me, but the truth must be known.

Coffee stunts the growth of children.

My grandmother was a firm believer in this lie. Therefore, I was forbidden to drink coffee until I was sixteen. Of course, I was sneaky and would drink coffee whenever I could without getting caught. I had an aunt who didn't believe this lie, and she had given all six of her children coffee without harming them. She used to sneak me some coffee when Granny wasn't looking. I have friends from Central America who tell me that coffee is an every-morning beverage for most children there; kids start drinking it when they're as young as three. Everyone there grows up just fine.

Apparently, this lie was started by C. W. Post (the cereal maker), who was trying to market his breakfast drink, Postum. His ad campaign warned

American parents of the evils of coffee because he was trying to shame them into switching their child's morning drink from coffee to Postum, which was made from wheat and molasses. Postum was much less healthy for children than good old coffee.



Sugar intake makes kids hyper.

There is a long list of valid reasons why I encourage you to limit your child's sugar intake, but this isn't one of them. This lie sprang from a letter written by a doctor and published in a pediatrics journal. No existing research supports this lie, although a great many parents (including myself) seem to see a correlation between sugar consumption and bad behavior. I also don't recommend giving children sugar close to bedtime.

Blood is blue until it's exposed to air.

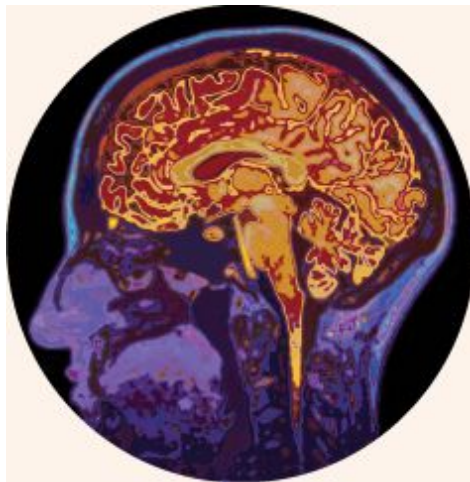
There are several versions of this lie, and all are untrue. Blood is always red. It's a brighter shade of red when it is carrying a full supply of oxygen (as it flows through your arteries), but it's still red when the oxygen has been used (as it flows through your veins). Blood appears blue in your veins because of the color of the vein walls.

Eating lots of carrots improves your night vision.

Raw carrots are fairly good for you, but no research supports the idea that eating carrots improves night vision. This rumor probably started as British propaganda during World War II to encourage citizens to eat root vegetables. Root crops eaten raw are full of fiber and good nutrition, but there is no evidence they improve your vision.

You are born with all the neurons in your brain that you'll ever have.

This terrible lie started long before we knew better. In the past, doctors, who had no research, believed that once you were grown, you could never form new neurons (nerve cells) in your brain. Good research has now proven that grown humans make new brain cells all the time. This is one of the reasons why eating a proper diet with plenty of healthy fats is good for your memory and lowers your risk of dementia. Your brain needs good nutrients to make new neurons. Some older doctors still believe this lie, but it has been completely disproved.



Ecstasy, meth, and some other drugs make holes in your brain.

Although these illegal drugs can have disastrous and permanent effects on brain function, none cause actual holes to form in the brain. I bet that this lie scares some kids into not trying drugs. However, you always should think about what might happen when your kids find out you lied to them. It is better to tell them the truth because it is as scary as the lie.

Brown sugar is better for you than white sugar.

I imagine this lie probably started because it resembles the stories that brown bread is better for you than white bread (a lie) and that brown rice is better for you than white rice (also a lie). Saying that brown sugar is better than white sugar is like saying unprocessed, organic poison is somehow better for you than processed poison. No, dummy; they're both poison.

Stretching before exercising prevents injury.

Every high school football coach in the world believes this lie is true, but it's not. Several studies have shown that stretching before physical activity doesn't decrease injury risk. It is, in fact, a waste of time. However, it does give football players something to do until the game starts.

Eating six small meals a day is ideal for managing diabetes or weight loss.

As with all the other lies, there is no research to back up this claim. Just like the *three square meals* advice of the past had no basis in research or medical fact, the idea of six small meals a day didn't have any scientific backing. You should eat as many times a day as you are hungry, whether this is once or four times. Eating six meals daily will keep your insulin level elevated and probably lead to weight gain. It's likely that you'll only get hungry six times per day if you're eating a high-carb, low-fat diet. Eating a diet with healthy fats produces a lasting sense of fullness, and you won't be hungry that often. Also, there is increasing research that shows that intermittent fasting (eating fewer meals each day) might be a much better strategy for long-term, meaningful weight loss.



Eating more protein makes muscles grow.

Protein doesn't make muscles grow unless you also are working out hard. Proteins are the building blocks of muscle tissue, but you must work those muscles to have muscle growth. Gorging on proteins does nothing but make your kidneys work hard to excrete the surplus protein and elevate your

insulin level. Unless you engage in resistance exercise, protein won't make your muscles grow.



Cracking/popping your knuckles will lead to hand/finger arthritis.

Multiple studies show this lie to be false. Popping your knuckles causes no damage to your joints; therefore, it doesn't lead to long-term problems. However, if someone in your life is annoyed by the sound of knuckle-cracking, please be considerate and lay off the snaps, crackles, and pops in that person's presence.





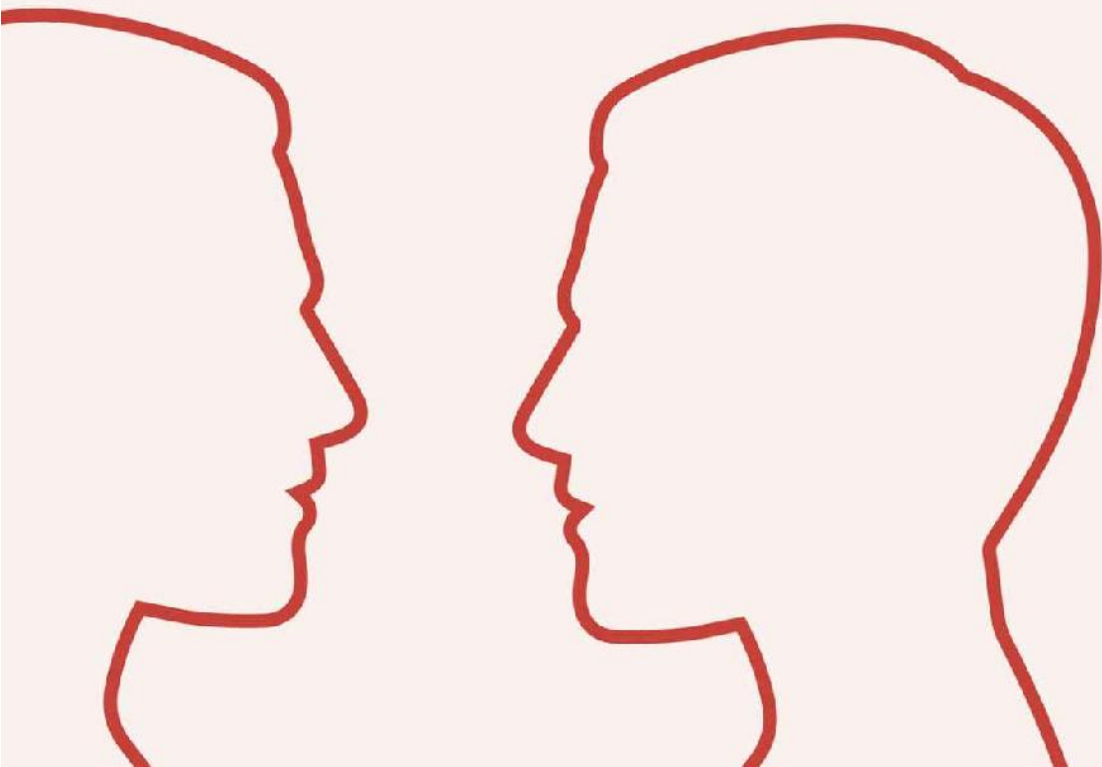
Do you have a little medical white lie that your doctor or someone else has told you? Send it to me at LMDTM@theberryclinic.com, and I might use it in my next book.





Chapter 26

DO AS I SAY, AND DO AS I DO



**You have a cough?
Go home tonight, eat a
whole box of Ex-Lax—
tomorrow you'll be
afraid to cough.**

—Pearl Williams



We've all heard some variation of the story of the preacher who told his congregation to follow the straight and narrow or face hell-fire and damnation. When confronted with the fact he was often seen in the bar drinking and smoking and flirting with women, he frowned and said, "You should do as I say, not as I do!"

Many doctors live and act just like this preacher, and it's disappointing. Some doctors use tobacco while telling you not to, and others are quite obese but still feel they have the right to tell you how to lose weight. Many doctors are unhealthy and unhappy, but they don't think twice about preaching to you about how to be healthy and happy. If your doctor doesn't put his health first, even though he possesses all the knowledge he supposedly does, then why should you listen to him? This is one of the greatest embarrassing questions of modern medicine. How can a doctor have any credibility at all if he does the very things he tells you not to do? Perhaps state medical boards should focus more on this type of bad behavior than on some behaviors they currently give lots of attention.

As I mentioned earlier, one day in 2008, I realized I was a fat, unhappy, and unhealthy doctor who spent five days of his week *teaching* patients to lose weight and be healthy. These unpleasant conditions had crept up on me slowly. I was busy with my family, practice, and community, and I gave little thought to my health and what kind of impression I was making on my patients. I was a former high school athlete who had become so fat I couldn't breathe while tying my shoes. I obviously had to do something. I had always been an athlete, so I decided I'd start jogging on the treadmill to get back into shape. I kept eating pretty much as I had been (which is to say I kept eating terribly), but I figured I'd burn off any extra calories with the increased exercise. My plan was to burn more calories than I ingested. Of course, in medical school I had learned that this type of calorie deficit should guarantee weight loss.

I started my new regimen and was doing pretty well in the exercise department, but after a month I had gained a pound instead of losing. That was the last straw. Even though no other doctor in my community seemed interested, I had always suspected there was more to nutrition than I had learned in medical school. I was beginning to believe the answer to my weight problem might somehow be connected to this deficiency in knowledge. So, like a good student, I hit the books.



I realized I was a fat, unhappy, and unhealthy doctor who spent five days of his week *teaching* patients to lose weight and be healthy.

I read a couple of the popular low-fat diet books and wasn't impressed. I then read *The South Beach Diet* and *The Atkins Diet*. They both seemed to make more sense than the low-fat diet books. I kept looking and eventually came across two other books: *The Primal Blueprint* and *The Paleo Diet*. These books were about both diet and lifestyle, and they made an incredible amount of sense. I capped off my reading with two more books about the Paleo/Primal diet, spent hours reading research studies on PubMed, and read several other books that seemed to be on the right track. The key concepts I came up with were not new. In fact, they were as old as the human species itself. These ideas were so old and seemingly forgotten that we were having to rediscover them. To many people, they seemed to be new, or even faddish, ideas.

I can summarize the concepts with these statements:

- We humans have been on this planet an incredibly long time.
- For 99.99 percent of that time, we never, ever ingested grains, sugar, or milk; we never drank fruit juices or high-calorie liquids.
- We lived mostly on fatty meat and green plants, seeming to prefer the fatty meat when we could catch it.
- To get the health, mind, and body we want, we must honor our past way of eating and living and realize that our DNA hasn't had time to catch up with all the starches, sugars, and grains we are taught to consume in our modern life.
- Your DNA responds to unnecessary sugars and starches by putting them right where you don't want them as adipose tissue on your belly, butt, and thighs.
- Your body also puts this adipose tissue in your liver, where it can lead to abnormal liver function and severe liver disease.

To achieve the health you want and the body and mind you desire, you have to honor certain things. The following sections describe some of those things.

HONOR YOUR HUMAN DNA

The DNA in your cells right now is the end product of more than 70,000 pairs of your ancestors reproducing successfully over eons of time. It should be difficult for you to think of yourself as a loser if you keep this fact in mind.

The DNA you've received from all those successful ancestors knows how to take care of itself; it likes certain things, it needs certain things, and it has no idea what to do with other things in your diet. Your DNA has become very good at working with and benefiting from your gut bacteria. Mutilating or mutating your bacteria with unnecessary antibiotics can have disastrous consequences on your health and your level of obesity. Your DNA needs certain nutrients to repair the cells and tissues of your body; otherwise, it can't optimize your body and your health.

Think about what your ancestors ate. That is what your DNA craves and what it knows how to use. Three major things your DNA has been exposed to only for the last few hundred years are grains, sugars, and the milk of another species. Most people across the world cannot drink milk without experiencing serious stomach upset. Their DNA doesn't code for the enzyme that breaks down the lactose in milk. Those of us who seem to be able to comfortably drink milk suffer more slowly and subtly from drinking it.

Feed your DNA what it has been eating the longest, and it will reward you with great physical and mental health. Your DNA and the parts of it that get turned on and off decide whether you will be healthy or not.

HONOR YOUR DIET

Your diet is the part of your environmental exposure that you have the most control over. You could organically grow every morsel of food that passes through your lips if you have the time, and you want to put effort into that endeavor. Because most of us are busy with other things, being organic farmers isn't usually an option. So, you have to do the best you can with the food you purchase and remember that you are literally made of what you eat.

What you eat and drink becomes *you*, and the old computer idiom of garbage in, garbage out (GIGO) is a good way to think of your diet. Not every bit of food you ingest will be pristine and organic. However, if you do the best you can to fill your belly with natural whole foods, your health and your life will benefit.

HONOR YOUR ENVIRONMENT

The environment you live in is filled with things you allow into it, and it's void of the things you keep out. Therefore, if you fill your environment with tobacco smoke, junk food, and lots of stress, don't be surprised if you lead a shortened and miserable life. Avoiding toxins such as tobacco smoke, unsafe water, and unsafe food additives are simple things you can do to protect your environment. It's important that you avoid BPA (bisphenol-A), which is in certain food and beverage containers. When you heat a container of food or beverage that has BPA in it, the BPA leaches into the food and drink, and it can cause problems with your glands and hormones. This is just one example of the many things harming your environment that you might not have heard about or that you've not given much thought to. Of course, you can't control every substance in your environment because there are just too many. But when you put effort into honoring your environment, you will be rewarded with better mental and physical health.



HONOR YOUR ACTIVITY

Although it's not a great method for losing weight, daily exercise is very good for your body and mind in many other ways. Studies have shown that being active benefits you both physically and mentally. When you go to the store, don't drive around for five minutes looking for the closest parking space. Park at the end of the lot and walk. Most of the time you'll get in and out of the store more quickly by doing this. You'll also save gas and keep

your mind and body in better shape. You can use little tricks like this to make your life a more active one without expending much effort or spending much money. Our ancestors walked a few miles each day, and sometimes they had to run very fast or lift heavy things. By making small efforts to do more of these activities in your modern life, you will replicate the lifestyle your DNA was accustomed to for thousands of years, and it will reward you for that. Don't waste time and money joining the gym unless you really love it and you have fun when you go there.

HONOR YOUR LAB WORK

After a certain age, you're wise to partner with an understanding, knowledgeable doctor and check meaningful lab values a few times each year. There are organs and systems in the human body that can start having subtle problems, and those problems worsen over years without causing any noticeable symptoms. Only with routine lab work can you and your doctor detect these problems early and correct them before you experience permanent damage. Many of the preventative tests recommended by the authorities serve little functional purpose; therefore, you must have a doctor you trust to guide you through the maze of medical testing options.



HONOR YOUR NEED FOR SCREENING

Early detection of diseases such as cancer greatly increases the chances that your doctor will be able to treat and cure them. Regular consultation with a trusted doctor leads to meaningful screening tests that identify early signs of cancer and other disease. Without a doubt, some screening tests are

overused, misused, or both, but the wise use of screening tests by a competent doctor can increase both your health span and your life span.

HONOR YOUR TELOMERES

Telomeres are little areas of DNA at the end of your chromosomes, and it appears that they protect your DNA from damage and quite possibly help keep you from aging more quickly than necessary. Studies show that avoiding things like smoking, processed foods, toxic chemicals, and bad stress helps keep your telomeres from shortening prematurely, which slows aging and keeps you healthier and more energetic. The study of telomeres and ways to optimize them is an exciting branch of medical research right now, and new developments in this area should yield significant health benefits for you.

HONOR YOUR MITOCHONDRIA

These little powerhouses inside your cells provide the energy that your cells need to perform their best. You have to feed your mitochondria the correct diet and protect them from toxins; otherwise, they will become weak and sick, and they'll start to dwindle in number. Protecting your mitochondria is yet another reason to avoid toxins in what you breathe, eat, and drink. Your mitochondria are your best friends if you want to stay active and vigorous into older age. Therefore, you should treat them right. Research into how to optimize mitochondria is another exciting branch of medical research that should uncover some benefits for your health.

HONOR YOUR STRESS AMOUNT AND TYPE

We all experience both good stress and bad stress. Good stress is beneficial to your body and mind; it comes from things like challenging yourself with difficult games, puzzles, and sports; learning new things; and going new places. Bad stress is harmful to your health, and you should minimize your exposure to it as much as possible. Bad stress comes from things like bad relationships, a job you hate, a sedentary lifestyle, or negative thinking. Although these things might seem trivial, it's important that you be mindful of these things and continually make your life a place you enjoy living.

HONOR YOUR GUT BACTERIA

You might think of your body as a single entity, but it's more than that. The medical community is becoming increasingly aware that your body is an orchestra of many players—both human and non-human. New research, for instance, is showing that the trillions of bacteria living in your intestines are vital to the quality of your overall health. Those mitochondria I discussed earlier were almost certainly bacteria we lived with harmoniously for so long that we invited them to move in permanently. Focusing all your effort and resources on something like joining the gym or taking expensive supplements is folly; those things will never lead to the long-term improvements in your health that you desire. Only when you honor all of the things I've listed will you achieve and maintain the mental and physical health you want and deserve.

HONOR YOUR SLEEP

We sleep for one-third of our lives. Although that may seem like a waste of time at first glance, good-quality sleep is intimately related to every facet of our health—both physical and mental. Protect your sleep environment like you would protect any treasure, and let nothing intrude.

Ensure your bedroom is as dark as possible. It should be cool and comfortable. Consider having only red light on in your bedroom after dark; alternatively, you could wear blue-blocking glasses. Only engage in pleasurable activities in your bedroom; never work, argue, or discuss difficult topics there. Have some form of white- or pink-noise source, so you are not awakened by bumps in the night. During sleep is the only time your brain activates the glymphatic system, which cleans, repairs, and renews your brain. Honor your sleep and protect your sleep environment.



Chapter 27

DEAREST COLLEAGUES



**Doctors always think
anybody doing something
they aren't is a quack;
also they think all
patients are idiots.**

—Flannery O'Connor



Shame on you. There was a time when almost everyone greatly trusted doctors. There was a time when doctors worked diligently to ascertain the truth for their patients, even if the truth wasn't what the patient wanted to hear. Doctors used to deliver bad news with the same discipline and character that they delivered good news. But some disturbing things have happened along the way. Doctors have become distracted and disenchanted, stopped paying attention, and—worse—stopped caring. Some of us have slowly morphed from healers and teachers into corporate medicine zombies and Big Pharma pill-pushers. I know this because I went down this road for a few years. I used to caution patients with diverticulosis about eating seeds and nuts, and I warned all patients to stay out of the sun. I used to tell patients to cut back on salt, and I wrote many high-dose statin prescriptions in my early career. But remember, dear colleague: We don't *do* medicine. We *practice* medicine. This means we are supposed to improve as the years pass. Are you improving in the advice and counsel you give your patients each year? (Hint: Knowing lots of details about the newest, expensive Big Pharma pill is not a sign of getting better at practicing medicine.)

There is redemption and forgiveness in every good story as long as it's deserved and earned. Your patients look up to you blindly and trustingly. They follow your advice in the face of facts and friends telling them to do otherwise. They are potentially harmed by your pills and your procedures, as well as by your indifference to the truth and your push for profit. You are well aware of your frustration, laziness, and ennui. The earned pride that you once felt and the deserving self-respect you once enjoyed are withering and crumbling.



There is often so much politics in medicine that being right can actually get you into trouble.

You hate the style of unthinking medicine you're practicing, and the patients don't like it either. They are being awakened by thoughtful, articulate experts in other fields of health, from herbal medicine to acupuncture. The Internet has given your patients access to more meaningful medical research and knowledge than ever before. Patients now have more medical research at their fingertips than the best of doctors used to have.

Despite how you might feel about that situation, it's a very good thing. If you found yourself with a case of cognitive dissonance from reading that last statement—or if you get upset when your patient brings printed info from a website when they visit you—then you have a problem. If you don't start righting past wrongs, there will soon come a day when you and your profession will be no more respected than politicians or used-car salesmen. You will lose your title of expert and healer, and you will be looked upon as pretentious and usually wrong. There are people who have no special training who post videos on YouTube that give better advice on nutrition and weight loss than you currently do. Every day, new videos are posted by people from all walks of life who have a greater grasp of nutrition, prevention, and how to apply both to real human problems than you do. If that last statement riles you up, then good. I want to piss you off, slap you around, and wake you up before you ruin the practice of medicine for all of us.

You are losing credibility. Patients once had only their doctor to go to with questions about their health and only their doctor to trust. There was no Internet, and the average town's library shelves had only a few dusty old medical books and journals. If a patient didn't believe the doctor, the person's only choice was to see another doctor, who usually was in another town. The odds were likely that the patient would hear the same verdict from the second doctor, and the matter was then settled. Only those with financial means could travel to larger facilities and specialists. Once there, they might receive better news or a different plan of care, but that wasn't always the case. Doctors didn't know everything back then either, but there was no way for patients to fact-check them.

Today it is different. Your patients can check the validity of your diagnosis on a website on their cell phones as they sit in your exam room. You might not have even finished your sentence yet. Your patients can consult experts from around the world via Skype and other services, and they can watch videos on the way to and from your office. Upon arriving home, patients can know just as much about their diagnosis as you do, and they might even discover that you don't know what you're talking about.

In this environment of increased information availability, we doctors find ourselves in both the scariest and the most exciting time to practice medicine. Merely wearing the white coat and draping the stethoscope over

your shoulders will not save you from the world of near-instant information your patients can access. If you thought you would comfortably cruise through your career in medicine, and no one would ever discover you had become intellectually lazy or had stopped caring, you were wrong. If you hope to remain respected and relevant, then you must read broadly and deeply, not only in your specialty and in your field but also in other fields. You can rest assured that your patient is reading opinions of their symptoms and conditions from experts in multiple disciplines because the information is supremely important to them. Understand this: Your patients don't care where they get good nutrition and wellness advice; they're just as happy to get it from the Internet as from you. If you're not willing to discuss their Internet research with them, distill it, add to it, and ultimately synthesize a working diagnosis with them, you will become as obsolete as a VCR player and as disrespected as an exposed charlatan. If, however, you choose to step up to this challenge, you will enjoy relationships of mutual respect with your patients that your predecessors would have only dreamed of. You will become a trusted and loved adviser, expert, and friend.

It's not too late. No matter how far you've allowed yourself to drift into frustration, laziness, and blind belief in what the American Academy of Whatever and the latest Big Pharma company-sponsored research tells you, you can turn your career around and move slowly but surely back to the rewarding and awesome career of being a doctor. If you're a specialist, don't fall blindly for the latest procedure, no matter how great the remuneration. If meaningful research doesn't show improved long-term outcomes from the new procedure, then don't perform it. If you're a primary care physician, don't fall for the catchy spiel of a smooth-talking drug rep without fact-checking the story for yourself. If you fail to do this, your patient's health and your reputation will suffer. You might be protected from professional sanctions by following the latest guidelines, but you will not be protected from the disgust and disenchantment your patients feel for you if the guidelines are later revealed to be folly. You may only remember your patients as a blur of humanity. Your patients remember you quite clearly as the doctor who either got it right or got it wrong.

Be very careful about repeating anything to your patients as medical fact if it hasn't been proven. Once a medical lie takes hold, it can take decades to remove it from our collective memory. An example is the lie that testosterone replacement will cause prostate cancer. This lie, as you may

know, began in the 1940s because of the belief of one respected and credible doctor. The misinformation quickly spread to the brains of all learned professors and teachers in the profession. They promptly passed the lie on to all their medical students (including you), who in turn spread it to the world as they began to practice. The fallacy quickly spread to the news media, who shared the information with everyone with a television or a magazine subscription. Most experts in urology now know that testosterone does *not* cause prostate cancer. However, a great many doctors, patients, and patients' families still believe it to be true. The quality of patients' lives and relationships are being negatively affected because of this sort of medical lie. Please verify that the advice you give your patients has been distilled through both common sense and meaningful research.

ADVICE FOR MEDICAL STUDENTS

M1 to M4: You've made it to medical school. Now, if you only had more hours in the day! I can remember sitting in my tiny library study room and thinking that if I took even a one-hour nap, it could lead to failure in pharmacology class. I feel your pain, but don't lose hope. Reading lots of research on various topics is not something you have time for yet. So, I want to share a few tips that will give you a much better chance of having a happy, successful practice when you get to that point. If you can ingest these few nuggets of knowledge and apply them to your present and future life, I think you will be a better doctor for it.

First, we are not even close to knowing everything there is to know about medicine, the body, and the mind. As you sit in your classes, you can get the impression that all has been discovered and written down about a given subject and that your professor plans to test you about all of it on the next exam. You do need to pay attention and do well in your classes, but you also need to remember your professors are human, fallible, and very proud of their positions in life. You just want to do well on your exams and get through this period with the best medical education possible. When you combine all the facts in the last two sentences and add lots of insecurities, fears, pressures, and dreams to the mix, you have a training plan that can lead you to being much less of a doctor than you could have been otherwise.

Helping people live the happiest and healthiest lives they can is an amazing career. Trust me; you want to be very good at it. By remembering a few key concepts now, you will be preparing yourself for success later.



Leeches were once standard of care. I say this to remind you never to forget that things you're taught are brilliant ideas today might be stupid tomorrow. The best doctors in the country once proudly used leeches to treat many diagnoses; leeches were the *standard of care*. If a doctor at that time had told other doctors who were using leeches it was stupid and dangerous, they would have run him out of town. Just because the American Academy of Whatever recommends doing or not doing something does not give you the leisure of leaving your thinking cap at home. You're responsible for your patients' health and helping them to prevent disease. The various guidelines are often published to stoke egos or plump up Big Pharma bank accounts. Sometimes standing up against something you think is wrong is scary and takes quite a bit of courage, but you went into medicine to be a hero and make a positive difference in your patients' lives, right?

Your professors are not gods, but don't argue with them in class. Lecture halls and medical journals are designed to appear as if the information they contain came down from on high. Your professor and clinical instructors are human, and they make mistakes. They're trying their best, but they might very well be repeating a medical lie to you as part of your education. Be alert for these lies, but don't point it out if you think you hear one. Overall, teachers don't appreciate being called out for being wrong, especially in front of the whole class. You are very busy and have little time for extra-curricular study, so if an instructor teaches you something that seems to go against common sense or the research as you currently understand it, file it away and research it more thoroughly when you get a chance.

Read the entire study, not just the conclusion. If you've ever seen a news report about a medical subject and thought the point the reporter was trying to make was silly, then you know what can come from reading only the conclusion of a medical study and then acting on it. Conclusions are in articles to save time for the reader—not for people to use to make medical treatment decisions. As you begin to read medical studies, pay careful attention to how often the conclusion doesn't follow from the findings or how the study design is flawed enough to give questionable results.

Always be looking for inconsistencies, but ask about them respectfully. Any time something said in lecture doesn't make sense to you or seems backward to your way of thinking, remember it. You might not have time to research it right now, but you will find the time later. Learned scholars behave this way. You should never blindly, dumbly accept what you are told, no matter how long the lecturer's white coat is. Look for inconsistencies now, but point them out later. Remember—you're trying to become a thoughtful, intelligent medical professional rather than an apostle who blindly follows a medical dogma.

You have a responsibility to know what you're talking about. When you become a doctor, you will be responsible for the professional advice you give your patients, and you're accountable for the outcome of bad advice. Make sure that your medical opinions and logic are rock-solid. You shouldn't just repeat what you've been taught; you should dispense advice based on what you have thought and what you have learned. There is a difference.

ADVICE FOR NEW DOCTORS

M-5 to M-9: If you're fresh out of med school, you have big ideas and big dreams for your future. As you're busy with your residency duties, or just finishing up, your present duties and future obligations take up almost your every waking minute. You've been in the game long enough to know that some attending physicians are very good at being doctors, whereas others are full of crap. You have to make it your mission not to become an attending physician who is full of crap. Let me give you a few suggestions to help you wind through this medical maze.

You have to look like you know what you're talking about but also always be doubting what you think you know. "Read or perish, reread or suffer," was the advice given to me early in my career by a respected mentor. There is a very fine line between exuding the confidence patients need to see in you to trust you, and in being a sophomoric, arrogant know-it-all. Walking this thin line will be part of your daily duty for the rest of your career. Doctors who are self-doubting in front of patients inspire no confidence, and doctors who act like they know it all, even when they don't, are dangerous. Be neither.

Patients don't esteem doctors for their actual ability because they can't truly know your ability; it's their perception of your ability that matters. Some of the worst doctors I ever worked with were held in God-like reverence by their patients. Conversely, some of the smartest doctors I've known didn't inspire confidence in their patients because those doctors weren't self-confident. Your goal should be to carry the perfect blend of public confidence and private self-doubt. This will make it easier for your patients to believe in you while at the same time enabling you to keep your clinical acumen sharp and ready. You owe it to yourself and your patients to keep reading, studying, and thinking.

Keep reading! I can't emphasize this point strongly enough. You must keep reading and learning; otherwise, your body of available knowledge, and the depth of your differential diagnosis, will shrivel over the years. Most of us have been around an older doctor who had neglected his reading for so long that he recognized only ten different diagnoses and prescribed the same five medicines. Don't be that doctor.

Read outside your specialty. It goes without saying that you need to stay current in your field, but your responsibility goes much further than that. Some of the most rewarding cases I've cracked came about because of something I had read about that was totally outside my specialty. To be truly helpful to your patients, you have to know a lot about a lot, whether you are a primary care physician or a specialist.

Read outside the field of medicine. Be an eager student with an unquenchable thirst for knowledge in all areas of life. There is an intellectual strength that comes from being widely and deeply read. Often, the only way to synthesize a difficult diagnosis is with knowledge from several sources,

and the key is sometimes knowledge you find outside the field of medicine. Remember, humans and their health are not separate from the rest of the world; they are right in the middle of it.

Shut up and listen to your patients, and they will tell you their diagnosis 90 percent of the time. I once heard a doctor tell a patient to stop talking so he could examine her and diagnose her condition. I was stunned by the ignorance of this statement. I thought he was joking at first, but he was not. You need to keep your physical exam skills honed, but make no mistake: Your most valuable tools are asking questions and listening to answers. The history you glean from listening to your patient is the key to diagnosis. Never forget that.

You will have hard days; suck it up. It's true that the doctor doesn't get to be sick. The doctor also doesn't get to be wrong. The buck stops with you, and it always will. You are ultimately responsible for every single thing that is done under your name and written above your signature. This is all the more reason to fill your head with knowledge and a differential diagnosis list as deep as the ocean.

ADVICE FOR YOUNGER DOCTORS

M-10 to M-15: Early in your practice, you have one million different things competing for your attention. You've made it through your training, and now you're trying to get the hang of being the doctor for your patients. Your practice is probably growing so quickly that you don't have much time to think of anything else. You squeeze in as much family and friend time as you can, but it's not enough. Let me share a few thoughts that might help you keep your head straight through this hectic time.

Keep reading! This is not optional. You have to stay abreast of the latest meaningful medical research. You can never lazily trust your patients' health to the opinion of older colleagues without verifying their recommendations against the research. Older doctors you will work with are often *right*, even when they're wrong. I was very bad at learning this lesson. You don't have to correct anyone else's paradigm; you are responsible only for yours. You have to show deference to older, respected doctors, even if they are wrong. Give them the respect they expect, while also protecting your patient from

the doctor's error. You don't have to publicly point out when an older colleague is wrong; you just have to make sure his error doesn't affect your patient's care. If you are not actively reading and thinking, you are slowly falling behind, and so is the treatment your patients are getting from you.

Be a leader in your medical community. The competition is gaining on you. Herbalists, chiropractors, naturopaths, and other alternative practitioners are gaining your patients' trust. The public is trusting these alternative practitioners more and doctors less. By reaching out to these practitioners and building a working relationship with them, you continue to lead your patients' medical care. Many a doctor has bluffed and blustered when asked by a patient about some alternative therapy, only to have that patient never return to their clinic again. You no longer have the liberty of pretending everyone else is wrong and you are right. Join with other practitioners and lead them, or be left behind.

Build and solidify your practice financially. You will be much more likely to make medical decisions based on how they will affect your income if your finances are tight. Don't be the doctor who orders a CBC on every single patient you see because you are trying to pay off your CBC-machine. Work to become independent both financially and clinically so your treatment decisions for your patients remain pure and unbiased.

ADVICE FOR OLDER DOCTORS

M-15+: You have had some degree of success in your medical practice. Over the years, you have come to feel that you can handle anything a patient might bring to you. Usually, after just a few words from a patient, you already know their diagnosis and what treatment they need. However, you then have to sit politely and let them finish their story before you can talk about their diagnosis and treatment plan. You have to remind yourself that sometimes hoofbeats are from a zebra because you now know how rare zebras are. This is a very dangerous time in your practice for you and for your patients.

If your career as a student is over, then your career as a doctor should be over as well. The reason I love the M numbering system is that it reminds me that I am still a student. (As I write this, I'm an M-21.) I am still learning—not just details, but whole new paradigms concerning medicine, nutrition,

and health. Reading and rereading are just as important for you now, my dear colleague, as they were when you were a lowly M-1. If you think you know everything there is to know, or even if you think you know all you need to know, you are a danger to every patient you treat. It's so easy to become complacent (lazy), jaded (bored), and burned out (done) that you can't bring yourself to question long-held truths and newly published ones. Well, tough. You chose to wear a title that means *teacher*, and you can't be a good teacher if you don't continue to be a good student. That doesn't just mean keeping up with the latest guidelines from your governing body. It means questioning both the old basics and the new guidelines.

Most patients believe the longer a doctor practices, the better he gets. However, you and I both know that isn't necessarily true, don't we? Only when a doctor continues to read, study, and think can this be true. The minute you stop having time to read, both in your specialty and outside of it, is the moment you start becoming less of a doctor. Neither your patients nor your nurse will necessarily see any sign of your stagnation or deterioration, but you and I both know it's true. Doctors have no real way of receiving meaningful social or peer feedback, and this can make it hard to stay on the proper path. It's easy for a seasoned doctor to bluff, pontificate, and confabulate in a way that makes him seem very impressive to all who hear. It doesn't mean that he knows or remembers a damn thing.

There is often so much politics in medicine that being right can get you into trouble because the right ideas seem so radical or go against the current standard of practice. Please don't be part of this problem. Step away from that dark side and be part of the solution. I've respectfully included several suggestions for you, the seasoned and respected doctor.

Keep reading. If macular degeneration steals your vision, then learn braille. Doing your reading is a requirement at any level of medicine. No matter your age or career status, books and journals will occupy much of your time if you're doing things properly. The doctor who is nearing retirement owes it to his patients to keep reading right up until the last day.

Know the guidelines, but don't blindly follow them. I'll bet that two hundred years ago, the American Association of Leech Medicine published guidelines on all the uses of leeches in medicine. Every doctor had a copy of these guidelines and followed them faithfully. If a doctor strayed from these

peer-reviewed guidelines, he would be censored or chastised by the powers that be.

Does that example sound ridiculous to you? Well, let's change the variables a little. Let's change the name of the association and the name of the treatment. The American Heart Association published guidelines on the use of statins in medicine. Every doctor had a copy of these guidelines and followed them faithfully. If a doctor strayed from these peer-reviewed guidelines, he would be censored or chastised by the powers that be. Same story, different players. The problem is that both these treatments, leeches and statins, were ill-conceived and continued to be *standard of care* long after it was clear that their use was foolish. They both offered little benefit to the average patient and were fraught with dangerous side effects.

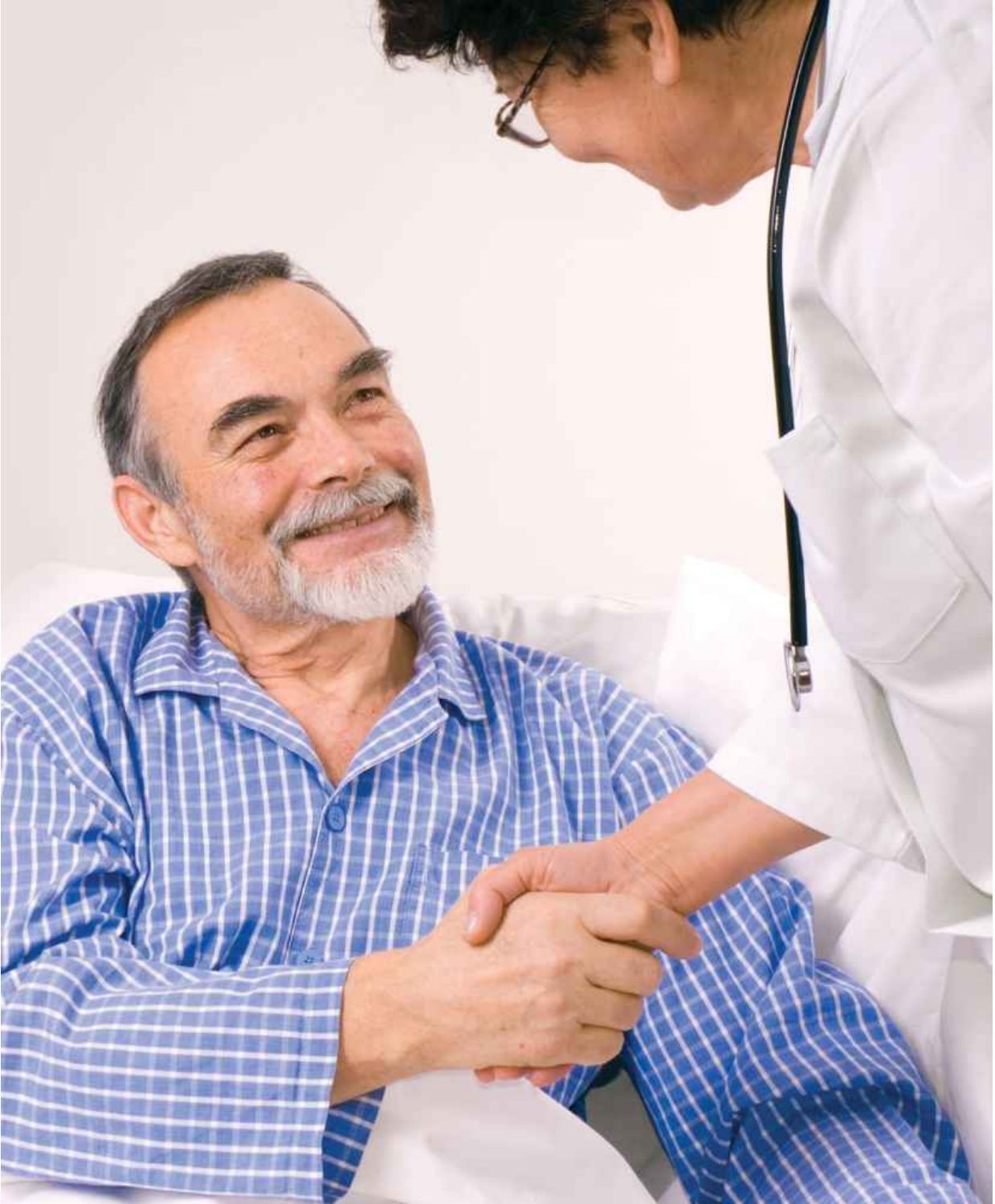
The lesson here is to stay up to date with the guidelines but don't follow them blindly. The statin fiasco didn't have to last decades; it could have been killed quickly if doctors had kept examining the research and asking questions. Millions of patients have suffered, and billions of dollars have been spent on a class of drugs that effectively did nothing positive for the average patient. This should get you thinking: What else are you prescribing that is ill-advised? Always be thinking and exploring the literature.

Your patients love and trust you; you owe it to them to be right most of the time. I have always thought of my patients as my children, although some people frown on this outlook. It helps me and the way my mind works to have this perspective, but it also holds me to a very high standard. For example, if the AHA says that the newest Big Pharma pill will lower the risk of something, but when you read the actual research, it's obvious that the right people at the FDA were treated to the right lunches, and that special treatment affected the outcome of the recommendation. What should you do? If you don't hold your patient in a special place in your heart (even the difficult patients), then you might say, "Hey, who am I to question the big dogs? I'm just a small-town doc, trying to get by."

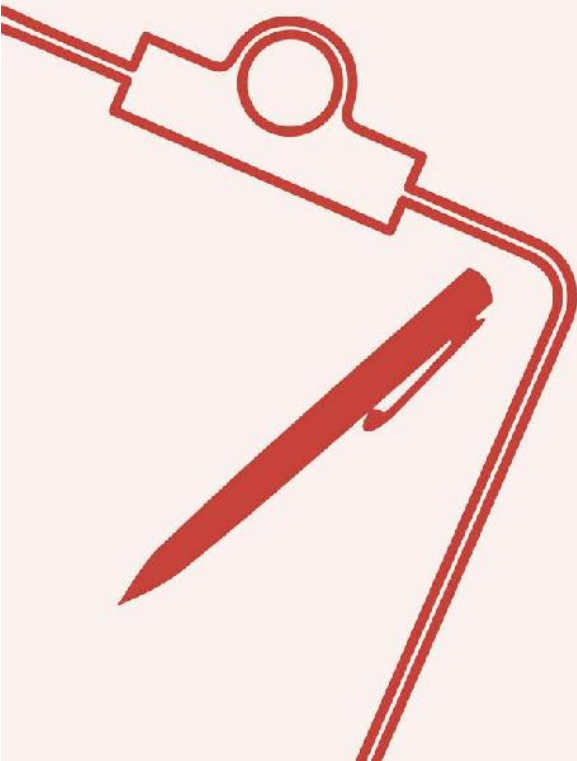
This rationalization might seem justified to you; however, it is one of the most shameful abdications of your position you could ever perform. Yes, you're between a rock and a hard place. Yes, there might be ramifications if you don't follow the guidelines. So what will you do? Thinking of my patients as my children makes it easy for me to tell the regulatory agencies to stick their guidelines up their... Well, I'll just say it makes it easy for me not to give my patient a pill fraught with side effects just because the big dogs

said I should. I wouldn't do that to one of my children, and I won't do it to one of my patients either.

Dear colleague, read, think, teach, and heal. Be a part of the renaissance of modern medicine, not a part of its demise.



EPILOGUE



**Here's good advice for
going into practice:
go into partnership
with nature;
she does more than
half the work and asks
none of the fee.**

—Martin H. Fischer



Congratulations. You have finished a book that was meant to change the way you think about your body, mind, and health. I hope you enjoyed it and learned a little something in the process. You must be wondering, “What should I do now?” Here are a few suggestions.

Do your homework.

At the end of each chapter, I named a book or website (or two) that I find to be useful for helping patients understand the concepts of the subject. Go back to the chapters that were most relevant to you and look for the homework sections. You will find that while doing your homework, you will come up with a unique plan for your health. It's up to you to decide which chapters are most important to you, and which homework assignments will help you most.

Decide whether you will keep your doctor.

Will you try to train the doctor you have now, or do you need to find a new doctor? This might be a very hard decision. You don't have to decide right now. A good way to help you decide is to take this book, or some pages from your homework, to your next appointment to see how your doctor reacts. If he's willing to listen and work with you, then he may be a keeper. Doctors can change, just like anyone else can. (Remember, I used to be a regular doctor who recommended a low-fat, whole-grain diet and prescribed statins left and right.) If, however, he reacts negatively and doesn't seem interested, then it might be time to do some doctor shopping. Finding a doctor who will be your partner in health is a priceless thing.



Start applying what you have learned to your life and the lives of your loved ones.

Every small improvement you make in your diet and lifestyle now can lead to huge rewards later. Stopping milk or having your testosterone checked can lead to more improvement in your life than you might imagine. Taking baby steps in the beginning is both expected and appropriate. You can take bigger steps as you grow in your newfound knowledge.

Take more responsibility for your health.

Keeping you healthy is neither your doctor's job nor your spouse's. It's *your* job, and you only get so many chances to work on it. You're made of what you eat, so eat the right stuff. Your brain is filled with the knowledge you put in it, so put in good stuff. Your life is filled with what you accumulate, so make sure you keep only what you really like.



Enlist your family and friends.

Being healthy is so much easier when those closest to you are also striving for good health. If your spouse or best friend isn't on the right track, then share this book with them or gift them a copy. It won't take long before your work toward better health produces results that others can see. When people ask what you're doing, tell them and explain why you're doing it.

Join with me on a journey to improve your body, mind, and spirit.

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Thank you so much for giving my book a chance, and I wish you the very best in health.



Fat and Cholesterol Don't Cause Heart Attacks And Statins Are Not The Solution

THINCS

The International Network of Cholesterol Skeptics
www.thincs.org

Paul J. Rosch MD, FACP
Editor

Fat and Cholesterol Don't Cause Heart Attacks and Statins Are Not the Solution

A Tribute to Uffe Ravnskov, MD, PhD
and his Establishment of THINCS,
The International Network
of Cholesterol Skeptics

Paul J. Rosch, MD, FACP, Editor

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Paul J. Rosch, MD, Editor

About The Editor

Paul J. Rosch, MA, MD, FACP is Clinical Professor of Medicine and Psychiatry at New York Medical College, Chairman of the Board of The American Institute of Stress and Honorary Vice President of the International Stress Management Association. He did his internship and residency at Johns Hopkins, and has a Workers Compensation subspecialty rating in cardiology, endocrinology and metabolism. In 1993, he began devoting a series of sessions on the fallacies of the lipid and diet-heart hypotheses at the annual Montreux International Congress on Stress that featured leading authorities from all over the world. This was long before the advent of THINCS and he was unaware of Uffe Ravnskov's contributions at the time.

Dr. Rosch is a Fellow and Life Member of The American College of Physicians, and has served as President of the New York State Society of Internal Medicine, President of the Pavlovian Society and Expert Consultant on Stress to the United States Centers for Disease Control. He has been the recipient of numerous honors here and abroad, including the Outstanding Physician's Award of the New York State Medical Society, the Innovation Award of The International Society for the Study of Subtle Energies and Energy Medicine, and The I.M. Sechenov Memorial Medal from The Russian Academy of Medical Sciences.

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Chapter One

Preface: Why And How This Book Was Written

Paul J. Rosch, MD

What Causes Heart Attacks?

If you ask anyone “What causes heart attacks”, the vast majority, including physicians, would undoubtedly blame high cholesterol from eating too much fat, or include this along with unavoidable influences like heredity and stress. That’s not surprising, since this dietary fat \Rightarrow elevated cholesterol \Rightarrow heart attacks scenario has been repeated over and over so many times for the past 70 years, that it has become accepted as gospel. As William James, the father of American psychology noted. *“There’s nothing so absurd that if you repeat it often enough, people will believe it.”*

But there was apparently nothing absurd about this. It was easy to visualize how fatty foods could elevate blood cholesterol, which was then deposited in arteries where they reduced and ultimately blocked the flow of blood. Animal studies seemed to support this sequence of events and large scale epidemiologic studies in different countries purportedly showed a close correlation between fat consumption and deaths from heart disease, and in some instances, with cholesterol levels. Proponents of this “Diet-Heart” or lipid hypothesis included eminent researchers and physicians who received the Nobel Prize, Lasker and other Awards for their contributions to this theory.

As a result, reducing fat intake, especially saturated fat, has been U.S. policy for the past 35 years. These official guidelines are the basis for determining the foods that will be used in the military, government cafeterias, schools, food assistance programs, industry food formulations, and restaurant recipes, as well as recommendations made by nutritionists and dieticians. And since they were also endorsed by leading authorities and prestigious organizations such as the American Heart Association and the American College of Cardiology, it was assumed that restricting fats

would provide cardioprotective and other health benefits. The advent of statins, which allegedly prevented heart disease by lowering cholesterol, appeared to prove the validity of the lipid hypothesis, and statins quickly became the best selling prescription drugs ever.

How Could We Have Been So Wrong For So Long?

The above erroneous beliefs began 100 years ago based on studies showing that feeding rabbits purified cholesterol obtained from egg yolks for two or three months produced lipid laden lesions rich in cholesterol in the aorta and other arteries. However, since rabbits are herbivorous, cholesterol is a foreign substance and blood levels were 4-5 times higher than those seen in humans. More importantly, these results could not be replicated in rodents or carnivorous animals so they were not relevant to humans. In addition, there was little clinical interest in any of the above, since prior to 1920, less than 10% of all U.S. deaths were due to heart disease.

That changed dramatically in the 1950s, when this had escalated to over 30% as an epidemic of heart attacks in middle-aged men was sweeping the U.S. This was also attributed to increased intake of fatty foods by Ancel Keys, after whom the K-rations used by US troops in World War II had been named. He demonstrated an almost straight line relationship between death rates from coronary disease to fatty food consumption in six countries, with Japan having the least and US the most. This was confirmed in his subsequent much larger Seven Countries study that showed heart attack and stroke death rates were also directly related to serum cholesterol levels and that saturated fats were the main culprit.

The problem was that although Keys had data on 22 countries, he cherry picked the seven that best supported his theory. When all the countries were included, there was no fatty diet-heart disease link, and **had he selected Israel, Sweden, Germany and France, he would have concluded that the more saturated fat consumed, the lower the incidence of coronary heart disease.**

Nevertheless, Keys was featured on the cover of the January 13, 1961 issue of *Time magazine*, was referred to in the media as “Mr. Cholesterol”, and triumphantly proclaimed, ***“No other variable in the mode of life beside the fat calories in the diet is known which shows such a constant***

relationship to the mortality rate from coronary or degenerative heart disease”.

The tremendous publicity given to his conclusions stimulated numerous attempts to reduce coronary disease by low fat diets. The Anti-Coronary Club Project launched in 1957 compared two groups of middle-aged New York businessmen. One group followed a “Prudent Diet” with corn oil and margarine instead of butter, cold cereal rather than eggs, and chicken and fish instead of beef. A control group ate eggs for breakfast and meat three times per day. The results published a decade later revealed that cholesterol levels of those on the Prudent Diet were slightly lower than the control group eating eggs and meat but there were eight deaths from heart disease compared to none in the high fat control group. In a final effort to prove his point, Keys fed middle-aged men a very high cholesterol diet but found that their blood cholesterol was no different than a control group who consumed less than half as much. Twenty years later, he was forced to admit, *“There’s no connection whatsoever between cholesterol in food and cholesterol in blood. And we’ve known that all along. Cholesterol in the diet doesn’t matter at all unless you happen to be a chicken or a rabbit.”*

The Framingham Study has had more of an impact on coronary heart disease research than any other epidemiological project. It was initiated by the NIH in 1950 to validate the lipid hypothesis by following 28,000 residents of Framingham, a small manufacturing town near Boston. It allegedly provided the first “solid evidence” that those with high cholesterol were at greater risk for heart attacks and that smoking and hypertension were also “risk factors” that had an additive effect. George Mann was involved early on to develop a nutritional survey to evaluate the effect of diet on cholesterol. An extensive analysis of the results completed by 1960 was never published, possibly because it found that participants had widely varying cholesterol levels and that *“something explains this inter individual variation, but it is not diet.”*

William Kannel, Director of the Framingham Study from 1966 to 1979, never referred to this, but told the press that the Framingham results essentially proved that cholesterol was a powerful predictor of heart disease, and coined the term “risk factor”. However, 30 years later the researchers found that **“For each 1% mg. drop in cholesterol there was an 11% increase in coronary and total mortality.”**

Although the study showed that a drop in cholesterol was associated with increased coronary deaths, it was cited as supporting the cholesterol-coronary link! What the public read in the joint AHA-NIH 1990 publication, *The Cholesterol Facts*, was, “**The results of the Framingham study indicate that a 1% reduction in cholesterol corresponds to a 2% reduction in CHD risk**”, and these words were followed by a reference to the Framingham-paper with the opposite result. It also stated, “The most important overall finding is the emergence of the total cholesterol as a risk factor of CHD in the elderly”. No data was presented to support this erroneous claim, since men over 47 with low cholesterol actually had mortality rates greater than those with elevated levels. The real truth about diet and cholesterol finally emerged in a 1992 editorial by William Castelli, who had replaced Kannel as Framingham Director in 1979, as follows:

Most of what we know about the effects of diet factors, particularly the saturation of fat and cholesterol on serum lipid parameters, derives from metabolic ward-type studies. Alas, such findings, within a cohort studied over time have been disappointing, indeed the findings have been contradictory. For example, in Framingham, Mass, the more saturated fat one ate, the more cholesterol one ate, the more calories one ate, the lower the person's serum cholesterol.

In a subsequent article Castelli stated that **nearly 75 percent of heart attacks were in people with normal cholesterol levels**. As indicated in the next chapter, a very recent study by Uffe Ravnskov co-authored by 15 physicians and scientists, many of whom have contributed to this book, demonstrated that senior citizens with high LDL-C live the longest.

The Tecumseh Community Health Study followed 2,000 men and women for two decades in an attempt to demonstrate that cholesterol levels were influenced by fat consumption in the previous 24 to 48 hrs. Based on data that included the composition of over 2,700 foods, it concluded that blood cholesterol and triglyceride levels were unrelated to the quality, quantity, or proportions of fat, carbohydrate, or protein consumed. **Those who ate the least amount of saturated fat had the highest blood cholesterol levels.**

The World Health Organization's MONICA epidemiologic project was undoubtedly the largest study ever designed to explore the relationship between risk factors and cardiovascular disease. It began in 1971 as a collaborative effort involving 32 centers in 21 countries that monitored

approximately 10 million men and women aged 25-64 for ten years. It thoroughly discredited the saturated fat–heart disease hypothesis. **All the countries in the top eight for fat consumption had lower death rates for heart disease than all of the eight countries that consumed the least fat.**

Such epidemiologic studies cannot disprove the fatty diet –heart disease hypothesis, nor can they prove it, as illustrated by Keys Seven Countries Study. They can only demonstrate whether there is a statistically significant association between the two, which is quite different. The only way to prove cause-effect relationships is a randomized clinical trial comparing the effect of restricting fat with a control group that followed their regular diet. As noted previously, the Prudent Diet study failed to show any such benefits, but it was limited to a relatively small number of middle aged men and there was little monitoring of what they actually ate. What was required were large scale interventional trials, and these have also failed.

The MRFIT (Multiple Risk Factor Intervention Trial) was the largest and most intensive effort to prove the links between diet, cholesterol and heart disease based on Framingham risk factors. Researchers carefully screened over 350,000 men at high risk for heart disease because they had elevated cholesterol, hypertension and smoked cigarettes. From this group, 12,866 healthy men aged 35 to 57 with no history or evidence of heart disease were enrolled in the study and randomly assigned to either an intervention group that received treatment for all risk factors or a control group that received usual care. A 1982 8-year follow-up revealed that cholesterol intake had been cut by 42%, saturated fat consumption by 28%, total calories by 21%, and there had been a significant reduction in hypertension and cigarette smoking in the intervention group, compared to usual care controls. Although there was also a modest fall in serum cholesterol, there was no effect on coronary heart disease and the disappointing conclusion was **“The overall results do not show a beneficial effect on Coronary Heart Disease or total mortality from this multifactor intervention.”**

The WHI (Women’s Health Initiative) study was established by NIH in 1991 to address the most common causes of death, disability and impaired quality of life in postmenopausal women. This 15-year \$625 million project involved 161,808 healthy postmenopausal women followed at 40 clinical centers that included a Dietary Modification interventional trial. It was designed to evaluate the effect of a low-fat and high fruit, vegetable and

grain diet on the prevention of heart disease, breast and colorectal cancers. Despite a modest lowering of cholesterol and diastolic blood pressure, there was no reduction in coronary heart disease in the low fat group.

Did Official Low Fat Guidelines Cause Our Obesity And Diabetes Epidemics?

It certainly seems to have been an important influence. Because of the low fat diet mandate, food manufacturers steadily eliminated or reduced fat as much as possible in all of their products. Supermarkets are now loaded with cookies, cakes, ice cream, soups, other canned foods and almost anything edible in order to display a prominent “Low Fat” and/or “No Cholesterol” label. The tacit implication is that you could eat as much of these low fat versions as you wanted because they were safe, or even healthy. However, removing fat detracted from their taste, so large amounts of fructose had to be added to make them appealing, especially for soft drinks. Fructose was subsequently found to have serious long term adverse effects such as developing metabolic syndrome (hypertension, increased abdominal fat, Type 2 diabetes, elevated triglycerides, low HDL) and increased risk of coronary disease. Many low-fat foods have increased amounts of sugar and other high glycemic index refined carbohydrates that promote obesity and diabetes. To improve shelf life, some also include artificial trans fats that also increase risk of coronary disease.

Nevertheless, low fat foods are still advertised as being “heart healthy.” A significant portion of the non-profit AHA (American Heart Association) income, which is now close to \$800 million/year, comes from its Heart-Check Certification Program that began in 1995. This allowed companies to advertise their products as “heart healthy” by displaying the AHA red heart with a white check mark logo. The first-year fee was \$7,500 per product and \$4,500 for annual renewals. Certification now costing up to \$700,000 has been extended to menus and restaurants, and the 700 or so certified products are in six categories that include different types of “Extra Lean” meat and seafood, certain nuts and grains, fish with a required level of omega-3 fatty acids, etc. Unfortunately, among those still endorsed are chocolate milk, high sugar breakfast cereals, processed meats full of chemicals and preservatives, as well as other products that are anything but

healthy.

It is no coincidence that the present obesity epidemic started precisely after these low fat guidelines were first published in 1980. The steady rise in obesity in the U.S. since then can be seen in Figure 1 from the CDC (Centers for Disease Control).

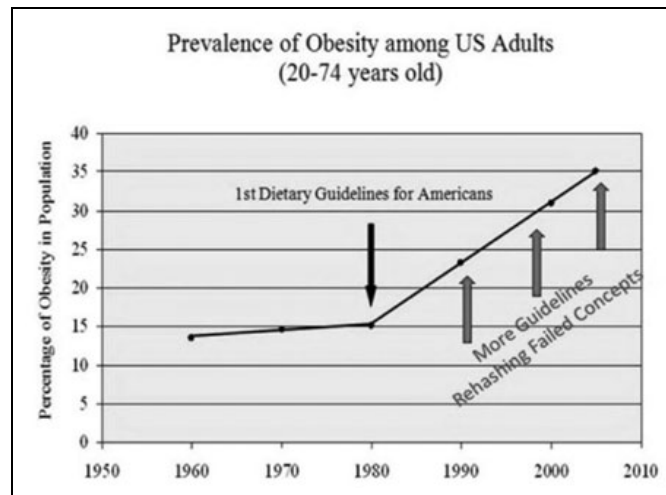


FIGURE 1 Increase in obesity following 1980 low fat diet recommendations

Advertising is crafted to be misleading. For instance, Welch’s “Healthy Heart” 100 % Grape Juice is a proud recipient of certification, but is sweetened with fructose. An 8-ounce serving contains 36 grams of sugar and 140 calories, about one-third more than the same amount of Coca-Cola. Their Concord Grape Juice Cocktail is only 25% juice and also contains high fructose corn syrup. The Academy of Nutrition and Dietetics, the “world’s largest organization of food and nutrition professionals” (formerly the American Dietetic Association or ADA), educates and licenses registered dietitians. Its largest sponsors include over a dozen junk food companies like Coca-Cola, PepsiCo and Mars that provide educational courses claiming that sugar is healthy for children. Coca-Cola spent \$3.3 billion on global advertising in 2013 to make people think that all calories are equal, sugared drinks are good for anyone who exercises, celebrity athletes drink them, so you should also. Many ads are targeted to children, who are particularly vulnerable to TV advertising and more apt to crave anything sweet. Coca-Cola advertising increased to an astounding \$4.3 billion in 2015 in an attempt to counter growing acknowledgement of its dangerous health effects.

The tragedy is that none of these low cholesterol low fat recommendations had any scientific support. It all began with the 1977 publication “Dietary goals for the United States” by the Select Committee on Nutrition and Human Needs chaired by Senator George McGovern.). The report was written by Nick Mottern, a former labor reporter for *The Providence Journal*, who had no scientific background and no experience writing about science, nutrition, or health. He relied heavily on Mark Hegsted, Professor of Nutrition at Harvard Medical School, who strongly believed that saturated fats from eggs and meat elevated harmful cholesterol levels, in contrast to monosaturated and polyunsaturated fats that might be beneficial. Mottern, a vegetarian, recommended that everyone should limit saturated fat intake to 10% or less, total fat intake should not exceed 30% and carbohydrates should be increased to 60% of daily calories. His report was not well received and there were objections from leading authorities like Rockefeller University’s Edward “Pete” Ahrens, and NHLBI Director Robert Levy, both of whom argued that nobody knew if eating less fat or lowering blood cholesterol levels would prevent heart attacks. The American Medical Association warned that the proposed diet raised the “potential for harmful effects” and others described it as a “dangerous public health experiment”. Dairy, egg, and cattle industry representatives from farming states, including McGovern’s own South Dakota, vigorously opposed the guidelines for other obvious reasons. The McGovern committee was due to expire at the end of 1977, and their report probably would have faded away, but the USDA (United States Department of Agriculture) was anxious to implement their recommendations, since a high carbohydrate-low fat diet would promote the sale of grains.

As a result, in 1980, the USDA and HHS (Health and Human Services) issued their first joint “Dietary Guidelines for Americans”, which adopted Mottern’s low fat high carbohydrate recommendations. This was the same low fat diet the American Heart Association had previously recommended for middle aged-men men at high risk of heart disease, without any proof that it was effective. A similar diet for everyone in the U.K. was proposed in 1983 but the only basis for this was Keys flawed Seven Countries Study, which stated that coronary heart disease “tended to be related” to serum cholesterol values and that, these in turn “tended to be related” to the proportion of calories provided by saturated fats in the diet.

These USDA and HHS “Dietary Guidelines” are reviewed and revised every five years but despite growing evidence that they were faulty, few changes have been made. The 2010 version claimed that “Lowering the percentage of calories from dietary saturated fatty acids even more, to 7 percent of calories, can further reduce the risk of cardiovascular disease.” As in the past, there was no reference to justify this. Moreover, a very recent **thorough meta-analysis of all the relevant randomized clinical trials prior to 1983 found nothing to support any relationship between dietary fat, serum cholesterol and deaths from coronary heart disease.** None of the trials included women and all but one was in middle-aged men with a history of coronary disease, so it was not known how this severe reduction of fat might affect children, women, or men in different age groups. In addition, none of these studies involved restricting saturated and total fat intake to this degree.

The sad fact is that this low fat diet should never have been introduced, and the consequences of this error have been disastrous. As shown in the graph above, only 15% of the population was obese when the low fat guidelines appeared in 1980. This has now increased to 35% in adults, and 17% in children and teenagers. If obesity rates continue on their current trajectories, 50% or more adults could be obese by 2030. And the diet heart idea has even had more catastrophic results.

Why Is There An Epidemic Of Type 2 Diabetes?

Type 2 diabetes was previously called “adult onset diabetes” to distinguish it from childhood, or insulin dependent diabetes. This term has been discarded, as it has been more and more common among adolescents and children, especially Hispanic/Latino and African Americans. It is well established that type 2 diabetes is a frequent complication of obesity, so it is not surprising that the obesity epidemic has been followed by a similar escalation in diabetes. As shown in Figure 2, from 1980 through 2014, the number of Americans with diagnosed diabetes has increased fourfold (from 5.5 million to 22.0 million). 40% of U.S. women and 17% of teenagers are now obese.

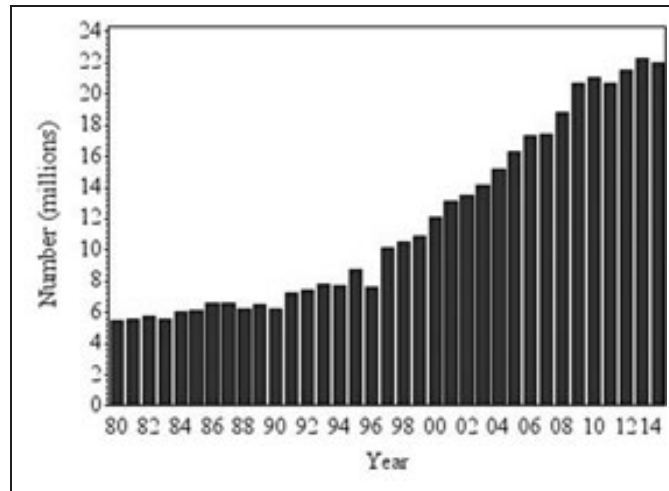


FIGURE 2 Number of U.S. Civilian, Non-Institutionalized Persons with Diagnosed Diabetes, 1980-2014. (Centers for Disease Control and Prevention, National Center for Health Statistics)

Type 2 diabetes is a serious condition because of its long-term complications, which include heart disease, stroke, retinopathy, kidney failure and peripheral arterial disease that can lead to amputations.

Why Have The Low Fat And Low Cholesterol Diet Recommendations Persisted?

Although leading authorities pointed out the fallacies and dangers of the diet-heart disease hypothesis and the need to lower cholesterol and LDL as much as possible, they soon found they could not get their views published or funding for their research renewed. One example was George Mann, Professor of Medicine and Biochemistry at Vanderbilt, a renowned nutritionist who was Co-Director of the Framingham Study in the early 1950s. Based on an analysis of the data he came to the conclusion that there was no evidence that higher fat intake or elevated cholesterol increased heart attacks or coronary mortality. His findings were never published since this contradicted what Framingham had been established to approve, and he quit in disgust. He subsequently showed that saturated fat was 66% of total calories for the Maasai in Kenya due to the consumption of large amounts of meat, milk and blood. Yet, heart disease was rare and cholesterol levels were about half those of the average American. In a 1977 *New England Journal of Medicine* editorial entitled “Diet-Heart: End of an Era”, Mann

documented the lack of relationship between diet and cholesterol levels, the lack of correlation between trends in fat consumption and death rates in the U.S. and the disappointing outcome of the cholesterol lowering trials with clofibrate and niacin. He referred to the American Heart Association and other panelists who had approved the low fat recommendations as “committee men” who essentially rubber stamped everything, and summed the situation up as follows:

The scientific issue was settled by majority votes. Galileo would have flinched. The dietary dogma was a money-maker for segments of the food industry, a fund raiser for the Heart Association, and busy work for thousands of fat chemists... To be a dissenter was to be unfunded because the peer-review system rewards conformity and excludes criticism.

As might be expected, this precipitated an avalanche of criticism from influential organizations, government agencies and their minions, as well as leading cardiologists, all of whom were strong proponents of the lipid hypothesis. Mann was vilified in the press, but these were mostly *ad hominem* attacks rather than any refutation of the supportive evidence he had cited. Although other experts voiced objections similar to Mann’s, they were also drowned out by the opposition and had little impact.

What the cholesterol crusaders desperately needed was something to show that lowering cholesterol reduced heart attacks. In 1984, their prayers seem to be answered with the publication of the NIH’s LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial) cholestyramine study. Cholestyramine binds to bile acids and since it is not absorbed, it is excreted along with the bile acids and blood cholesterol falls. After three years of screening 480,000 applicants, 3,806 men aged 35-59 with a serum cholesterol over 265 mg/dL and no history of heart disease were recruited. Half were treated with cholestyramine, half received an equally unpleasant tasting placebo and both groups followed a “moderate cholesterol lowering” diet that limited fat intake. It had been predicted that taking cholestyramine daily for seven years would lower LDL cholesterol by 28% and result in a 50% reduction in significant coronary events. At the end of the study, although there was only an 8% fall in total cholesterol and a 12% drop in LDL the sponsors triumphantly claimed a 19% reduction in risk for coronary events in the cholestyramine group. This allowed Basil Rifkind, the director, to claim “for each 1% reduction in cholesterol, we can expect a

2% reduction in CHD events”, implying a causal relationship rather than a statistical association. The statement was widely circulated in the media, even though it was not valid, since a subsequent review of the data found no difference in CHD events between the two groups. More importantly, 19% was a relative risk reduction. The absolute or actual risk reduction was 1.1% for all coronary events, and for fatal heart attacks, it was only 0.6% and without statistical significance, because the authors had used the one-sided t-test, an incorrect statistical method.

In addition, the cholestyramine study dealt mainly with individuals with familial hypercholesterolemia, a lipid disorder affecting fewer than one in five hundred. It was uncertain that lowering cholesterol would be beneficial for men in other age groups or women of any age, or whether cholestyramine would be safe, or even tolerated. Some men stopped taking the foul tasting four or five packets of cholestyramine after a few days, and many complained of severe constipation and other gastrointestinal complaints due to the lack of bile acids. Most were unable to take the full 24 grams daily, so that relatively few stayed on the required regimen for seven years. With respect to safety, cholestyramine interferes with the absorption of fat-soluble vitamins and numerous common drugs, including Coumadin, Digoxin, Inderal phenobarbital, thiazide diuretics and thyroid. As indicated, there was no statistically significant difference in heart attacks between the two groups and their overall mortality rates were essentially the same. However, there were more deaths from cancer, intestinal disease, stroke, violence and suicide in the cholestyramine group. Little mention was made of this, or the 21 cases and 8 deaths from gastrointestinal cancer in those taking the drug, compared to 11 cases and only 1 death in the control group.

There was so much criticism of this trial that an NIH-sponsored National Cholesterol Consensus Conference was assembled in late 1984 to evaluate the numerous complaints. Although dissenters were allowed to speak briefly, their comments were not included in the final report, which had apparently been prepared in advance with a few blanks to fill in numbers. One of these was 200 mg/dl to indicate that anyone with a cholesterol over this was “at risk”, when everyone had previously agreed that the upper limit of normal was 240 mg/dL Prior to that it had been 280 mg/dL and this new arbitrary reduction would put most adult Americans “at risk”. The major

conclusion of the NIH Consensus Panel published in the *Journal of the American Medical Association* that was widely referred, to was, **“It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels (specifically, blood levels of low density [LDL] cholesterol) will reduce the risk of heart attacks caused by coronary heart disease.”**

Although the LCR-CPPT was a drug, rather than a diet trial, the investigators and their sponsors made the unwarranted claim that if lowering cholesterol with a medication could prevent heart disease, lowering cholesterol by reducing fat intake would have the same result. This led to an enormous public relations campaign to convince the public as well as physicians that avoiding dietary fat was crucial to prevent and treat coronary disease. The NCEP (National Cholesterol Education Program) was established under the auspices of NHLBI (National Heart, Blood, and Lung Institute) to meet on a recurring basis, review pertinent scientific research and make recommendations about ways to reduce coronary disease. A large “Physicians Kit” was sent to all doctors in America, compiled in part by the American Pharmaceutical Association, whose representatives served on the NCEP coordinating committee. It emphasized the importance of cholesterol screening, the advantages of cholesterol-lowering drugs, the unique benefits of the Prudent Diet and the use of margarine rather than butter. September was designated National Cholesterol Education Month, during which everyone is urged to have their blood cholesterol and other lipids checked and to take steps to correct any abnormalities. These activities were promoted by NIH, NCEP, AHA, USDA, numerous other medical organizations and low fat food manufacturers in an unprecedented, massive advertising blitz.

Manipulating Data, Dirty Tricks And Deceptive Advertising

This evoked even more criticism, that now included some previous lipid hypothesis proponents, like Michael Oliver, who first showed that coronary heart disease patients were more likely to have abnormal levels of blood lipids than matched controls. In a *Nutrition Today* editorial, George Mann again summed things up:

*Saturated fat and cholesterol in the diet are not the cause of coronary heart disease. **That myth is the greatest scientific deception of this century, perhaps of any century.** The diet-heart hypothesis has been repeatedly shown to be wrong, and yet, for complicated reasons of pride, profit and prejudice, the hypothesis continues to be exploited by scientists, fund-raising enterprises, food companies and even governmental agencies. **The public is being deceived by the greatest health scam of the century....**They have held repeated press conferences bragging about this cataclysmic break-through which the study directors claim shows that lowering cholesterol lowers the frequency of coronary disease. They have manipulated the data or reached the wrong conclusion....The managers at NIH have used Madison Avenue hype to sell this failed trial in the way the media people sell an underarm deodorant.*

This and numerous other complaints were drowned out by the propaganda promulgated by the cholesterol cartel of manufacturers of low fat foods, cholesterol lowering drugs, lipid testing equipment and other vested interests. In addition, anyone who jeopardized their lucrative profits was swiftly and severely punished.

For example, Mann was determined to bring this issue before the public by organizing a conference of leading authorities who supported his views in Washington, D.C. In his invitation, he wrote, “Hundreds of millions of tax dollars are wasted by the bureaucracy and the self-interested Heart Association.... Segments of the food industry play the game for profits. Research on the true causes and prevention is stifled by denying funding to the ‘unbelievers’. This meeting will review the data and expose the rascals.” When the cholesterol cartel, or “Heart Mafia” as Mann called them, learned about this, they sent out false press releases to speakers and other invitees that the conference had been canceled. Speakers were also phoned and warned that their funding would be canceled or their academic status would suffer if they participated in such an event. Many backed out and the Greenwall Foundation, which had promised to fund this event, also reneged. Mann eventually funded the conference himself, but there were only half- dozen or so speakers, and he told the audience:

You will see that many of our contributors are senior scientists. They are so for a reason that has become painfully conspicuous as we organized this meeting. Scientists who must go before review panels for their research funding know well that to speak out, to disagree with this false dogma of Diet/Heart, is a fatal error. They must comply or go unfunded. I could show a list of scientists who said to me, in effect, when I invited them to participate: ‘I believe you are right, that the Diet/Heart hypothesis is wrong, but I cannot join you because that would jeopardize my perks and funding.’ For

*me, that kind of hypocritical response separates the scientists from the operators, the men from the boys...Those who manipulate data do not appreciate that understanding the nature of things cannot be permanently distorted – the true explanations cannot be permanently ignored. Inexorably, truth is revealed and deception is exposed.... **In due time truth will come out.** This is the relieving grace in this sorry sequence.*

Kilmer McCully's discovery of the contribution of homocysteine to coronary heart disease suggesting that it could be more important than cholesterol and might be easily prevented by inexpensive B vitamins, also brought swift and vicious retaliation. Funding for research disappeared leading to the loss of his laboratory at Massachusetts General Hospital. The hospital Director told him to leave and "never to come back" and his Harvard affiliation and tenure were also terminated in 1978. When subsequently interviewed about his research on a TV program, he promptly received a phone call from the Public Affairs Director of the hospital who told him to "shut up" and that "they didn't want the names of Harvard and Massachusetts General Hospital to be associated with my theories." Although obviously well qualified for many positions that were being offered, and despite the fact that he did well on numerous interviews, he was unable to find employment for two years.

When McCully and those who had recommended him made appropriate follow-up inquiries they ran into a stone wall of silence. However, repeated rumors of "poison phone calls" from Harvard began to surface and it was only after a leading Boston attorney threatened a lawsuit that things suddenly changed, and despite previous rejections, he was able to resume his research at the Veterans Administration Hospital in Providence, Rhode Island. Since then, the association between elevated homocysteine and heart attacks, stroke, and accelerated atherosclerosis has been repeatedly confirmed, as well as links to other disorders.

Uffe Ravnskov's book *The Cholesterol Myths* was actually burned on a 1992 Finnish television show because it was a scathing and devastating indictment of the numerous flaws in the lipid hypothesis. Since none of the well documented claims could be refuted, critics resorted to this medieval practice to retaliate. Although Uffe escaped being burned at the stake, his e-mail was later hacked and "spoofed" and he has been harassed in other ways.

Other examples of skullduggery, dirty tricks and deceptive practices could be cited, especially with respect to the safety and efficacy of statins. Cholesterol proponents proclaimed they had now proven their claims with the November 19, 1994 *Lancet* publication of the Scandinavian Simvastatin Survival Study, often referred to as the 4S study. It involved assessing the effect of simvastatin on morbidity and mortality in 4,444 heart attack patients aged 35-70 with elevated cholesterol levels. Half were treated with simvastatin (Zocor) and half with a placebo. At the end of 5.4 years, LDL had been lowered by 35%, cholesterol by 25%, and only 5% in the treated group had died from a heart attack, compared to 8.5% of the placebo controls. The reduction in nonfatal heart attacks was even more impressive, 15.9% vs. 22.6% in controls and for strokes, it was 2.7% compared to 4.3% for controls. Unlike previous cholesterol lowering drug trials, there was no apparent increase in adverse side effects. Michael Oliver, a leading authority, urged physicians in the *British Medical Journal*, “*Lower patients’ cholesterol now! There is no longer any doubt about the benefit and safety of treating hypercholesterolemia in patients who have had a myocardial infarction.*”

The fact is that none of the subsequent statin trials showed similar rewards in patients with a history of heart disease. None of them has succeeded in lowering mortality by more than 2 % and only for patients with previous cardiovascular disease. No trial has succeeded in lowering mortality in people without heart diseases, in women or in senior citizens, so why prescribe them for everyone or put them in the drinking water as some enthusiasts had suggested.

However, as documented in the following chapters data are manipulated in company sponsored drug trials in order to conceal or minimize the adverse side effects of statins or exaggerate their benefits. The results were often presented to physicians in a similarly deceptive fashion as were television and media advertisements to the public. For example, the 42% reduction in risk of cardiac death in the simvastatin study was relative risk, whereas the absolute risk reduction was only 3.5%. The TV commercials for atorvastatin (Lipitor) featuring Dr. Robert Jarvik, identified him as the inventor of the artificial heart. Jarvik tells viewers that as a cardiologist, he takes Lipitor and prescribes it for family members. He is shown vigorously and adroitly sculling a boat over a serene lake into the sunset as proof that

Lipitor has kept his heart in excellent shape. The facts are that Jarvik is not a cardiologist and could not prescribe anything since he does not even have a medical license. He had no experience sculling and the muscular frame viewers saw rowing away was that of a stunt double who was an expert sculler. Although he made some subsequent revisions, he did not invent the artificial heart and there is no indication that he took Lipitor prior to the guaranteed \$1.35 million for serving as pitchman. Pfizer withdrew the ad following a Congressional investigation, but it continued to merchandize Lipitor with some \$250 million a year in commercials that generated \$11 billion a year in sales, more than any other pharmaceutical in history.

The Relative Risk, LDL “Bad Cholesterol” and HDL “Good Cholesterol” Fiascos

Lipitor print ads featuring Jarvik persisted, such as this *New York Times* commercial “In patients with multiple risk factors for heart disease, LIPITOR REDUCES RISK OF HEART ATTACK BY 36%. * But 36% of what? The asterisk explains this in mice type at the bottom of the page as follows: “That means in a large clinical study, 3% of patients taking a sugar pill or placebo had a heart attack compared to 2% of patients taking Lipitor.” The 36% was relative risk and the absolute risk reduction of only 1% was not mentioned. **In other words, if you take Lipitor daily for years, your risk of having a heart attack drops 1%, and this is only if you have risk factors such as family history, high blood pressure, age, low HDL (“good” cholesterol) or smoking.** Another Jarvik/Lipitor Times ad proclaims: “In patients with type 2 diabetes, LIPITOR REDUCES RISK OF STROKE BY 48%* In this instance, the asterisk refers to the following mice type explanation, “That means in a large clinical study, 2.8% of patients taking a sugar pill or placebo had a stroke compared to 1.5% of patients taking Lipitor.” The absolute risk reduction here is 1.3% and this is also only in patients at increased risk due to other influences. The fact is that statins increase risk of developing diabetes, and not only do not prevent strokes, but can actually increase those due to bleeding.

The problem here is that lowering cholesterol or LDL (“bad cholesterol”) has been accepted as a surrogate for preventing heart attacks, even though this has never been proven. In addition, when most people read that Lipitor

reduces risk of stroke by 48%, they think this means it will cut the likelihood of a stroke almost in half. No association between cholesterol levels and the degree of atherosclerosis has ever been found in postmortem studies of the general population, and no clinical or imaging study has found any relation between the degree of cholesterol lowering and improvement. **In one angiography study in which blood cholesterol had been reduced by more than 25% in 26 patients, atherosclerosis was increased in 18 and unchanged in the remainder.** No correlation has ever been found between cholesterol levels and the degree of coronary calcification or peripheral atherosclerosis. High cholesterol does not increase risk for heart attacks in people older than 60, healthy women of any age, nor in patients with diabetes or renal failure. Senior citizens with high cholesterols are protected against cancer, have significantly fewer infections and live longer than low cholesterol controls. At least half of heart attack patients do not have elevated levels of cholesterol or LDL and two studies found that cholesterol and LDL were lower than normal in those admitted for acute myocardial infarction. In one of these in which patients were followed for 3 years, mortality was highest among those with the lowest cholesterols. In familial hypercholesterolemia, there is no correlation between the very high cholesterol (1,000 or more) and LDL levels (over 250) and any increased incidence or severity of coronary disease.

As the insignificance of cholesterol as a cause of coronary atherosclerosis became increasingly obvious, emphasis shifted to LDL as the culprit. This had its origin in the 1984 statement, *“The more LDL there is in the blood, the more rapidly atherosclerosis develops”* by Nobel Laureates Michael Brown and Joseph Goldstein. Nevertheless, the vast majority of statin studies do not show that the degree of atherosclerosis or its severity is related to either LDL levels or the magnitude of their reduction with statins. Lowering LDL “bad cholesterol” as much as possible does not prevent heart attacks in healthy people. Adding ezetimibe, which blocks absorption of cholesterol to simvastatin, resulted in a greater lowering of cholesterol, triglycerides and LDL and significantly raised HDL. However, it showed no reduction in coronary events or mortality and was associated with a possible increase in cancer. Clinical trials of torcetrapib, a drug that raised HDL “good cholesterol” had to be stopped because of an increase in cardiac

death rates and hypertension.

But things may be much more complicated, since particle size may determine whether LDL might be good and HDL might be “bad”. Light and fluffy LDL particles actually appear to be associated with a lower risk of heart disease, probably because, as documented by Ravnskov and McCully, they participate in the immune system. Furthermore, as indicated previously, elevating HDL with drugs actually increased cardiac mortality and some individuals with very high HDL also have increased atherosclerosis. A recent study suggests that this paradox is due to a genetic defect that produces an excess of large HDL particles that are harmful. Thus, **we now have to contend with bad LDL that is good, and good HDL that is bad.**

Truth Will Out And The Times They Are A Changin, But Is It Too Little, Too Late?

There may be some light at the end of the tunnel, since as Shakespeare noted and George Mann predicted, “truth will out”. Faced with overwhelming evidence that a high fat diet did not cause heart attacks, the latest official guidelines finally acknowledge that “cholesterol is not a nutrient of concern for overconsumption”, although saturated fat is still limited. And the most recent American College of Cardiology and American Heart Association guidelines have abandoned lowering LDL and cholesterol as much as possible as the goal of statin therapy, since any benefits are unrelated to their concentrations. On the other hand, none of these changes will decrease statin sales since the new recommendations are to treat individuals at high risk rather than high cholesterol. This would include everyone with existing heart disease, an LDL of 190 mg/dL or higher and all type 2 diabetics between 40 and 75 years of age regardless of LDL or cholesterol levels. In addition, anyone aged 40 to 75 with a 10-year risk of heart disease that is 7.5 percent or higher using a risk calculator with arbitrary values based on age, gender, race, cholesterol, HDL, blood pressure and smoking. **As a result, 13 million more Americans will now be eligible for statins, including 97% of senior citizens, despite evidence that this would do more harm than good,** as will be seen in the next chapters. Almost 20% of patients experience statin side effects, and

although the vast majority stop taking them, it may be too little and too late for some. A recent study of physically active healthy people who took statins for 90 to 365 days reported that their **risk of developing diabetes and diabetic complications doubled over the next five years compared to controls**. Short term statin use was not associated with any decrease in cardiovascular events, so for healthy people in particular, statins can do more harm than good, especially since type 2 diabetes is a significant risk factor for heart disease.

It would appear that the lipid hypothesis will continue to persist and prevail as long as it remains profitable for statin and low fat food manufacturers and other vested interests. A good example of this are the recently approved PCSK9 inhibitors, Sanofi-Regeneron's Praluent (alirocumab) and Amgen's Repatha (evolocumab). These monoclonal antibodies, which lower LDL by helping the liver to remove it, are indicated for the treatment of heterozygous familial hypercholesterolemia and heart attack and stroke patients who have not been able to lower LDL to satisfactory levels despite maximal statin dosage. The drugs are given by injection every two weeks, or in some cases once a month and were initially projected to cost over \$14,000/year, although this may have changed. They are covered by most insurance and Medicare plans but co-payments can vary. The competition is so keen that Sanofi-Regeneron paid \$67.5 million to speed up approval of Praluent so that it would be available before Repatha. Both drugs are given as **an adjunct to diet and maximal statin dosage**. No significant adverse effects have been noted but there are no long term follow-up studies, and some clinical trials have shown that neurocognitive side effects are double those in controls, but this is only a 1% absolute risk increase.

The issue here is that these drugs have been approved solely on the basis of their ability to lower LDL rather than reduce or prevent coronary events or mortality. This, despite the fact that lowering LDL or cholesterol as much as possible has been abandoned as a goal of statin therapy. Praluent's hook phrase is "the fall of high cholesterol" and 2-page ads in *Time* and *People* magazines explain that "When diet and the highest tolerated dose of statin are not enough, PRALUENT will make it PLUNGE". It shows a happy middle-aged male whose LDL dropped from 126 to 68. The ad does include in tiny print the following sentence "The effect of Praluent on heart

problems such as heart attacks, stroke, or death is not known.” This means that patients who had stopped statins because they failed to reduce LDL sufficiently, will be encouraged to resume maximum tolerable doses along with with Praluent injections, even though there is no evidence this will provide any cardiovascular benefits. In addition, once a drug is approved by the FDA as being safe and effective for a specific indication, it can be prescribed for any condition if a physician feels it could be beneficial. It has already been suggested that Praluent should be useful in myocardial infarction and acute coronary syndromes and the 18,000 patient ODYSSEY trial may determine this when the results are released in 2017. As with Humira (adalimumab) and other therapeutic monoclonal antibodies, resistance may develop or there can be adverse immune system responses. Nevertheless, more drugs are in the pipeline. Pfizer’s PCSK9 inhibitor, bococizumab has already completed two phase 3 trials showing that is superior to a placebo for lowering LDL, including patients taking statins.

CETP (cholesterol ester transfer) inhibitors, which increase HDL and lower LDL have not lived up to expectations., Lilly’s 12,000-patient phase 3 trial with evacetrapib was suddenly halted last October since it showed no reduction in rates of heart attack, stroke, or cardiovascular disease, despite positive effects on lipid levels. Prior to that, Pfizer’s \$800 million torcetrapib study was discontinued because of increased death rates in the treatment group. Nevertheless, Merck’s anacetrapib, which raises HDL and lowers LDL, may be approved in 2017 if there are no safety concerns, regardless of whether it provides cardioprotective benefits.

Why And How This eBook Was Assembled To Honor Uffe Ravnskov And THINCS

In 2014, I was invited by the senior editor of *Expert Review of Clinical Pharmacology* to serve as Guest Editor for their March 2015 special focus issue. These deal with important or controversial issues and generally consist of 7-9 review articles (5000 to 7000 words) and 1 or 2 Editorials (up to 1500 words). The topic I selected was the lipid hypothesis of coronary heart disease, which was not only important but extremely controversial. I had devoted several days to exposing its flaws at the annual International Congress on Stress in Switzerland 2 decades earlier that included George

Mann, Bill Stehbens, “Pete” Ahrens, Ray Rosenman, Stewart Wolf and other critical luminaries. The subsequent 2000 publication of Uffe Ravnskov’s *The Cholesterol Myths* in English had exposed and convincingly documented numerous additional fallacies. He had also established THINCS (The International Network of Cholesterol Skeptics), which grew to include 100 physicians, scientists and others who opposed the entrenched fatty food and cholesterol cause of heart disease dogma. It was a challenge to draw up a Table of Contents since there was such an embarrassment of riches and so many important facets of this topic that it was difficult to cover everything in the limited space available. I explained this and the editor agreed that I could choose my own format as long as I did not exceed the 80,000-word count limit. My tentative title for this special focus issue was “Why Cholesterol And Lipids Don’t Cause Coronary Heart Disease And Statins Are Not The Solution.” In addition, it was designed to honor Uffe Ravnskov for his seminal efforts in demonstrating these claims and for his establishment of THINCS, The International Network of Cholesterol Skeptics.

I had an enthusiastic response and in October 2015, submitted 12 papers for peer review. Both the editor and I thought these were of high quality, and were surprised that even after being revised to satisfy peer reviewer concerns, only three were accepted. I attributed this to bias and in some cases ignorance. Fred Kummerow had “too many self-references” despite the fact that he has written extensively about the dangers of trans fats for over 50 years and finally sued the FDA successfully for failure to warn consumers and physicians about this. Others who had previously published papers on their topics were accused of self-plagiarism, an oxymoron, and I was severely reprimanded for questioning the conclusions of Ancel Key’s flawed Seven Countries study. Beatrice Golomb’s state of the art contribution on what the new recommendations should be for statin therapy had “too many references” and Duane Graveline’s account of his global amnesia experience and the thousands of confirmations he received from others about memory loss and neurocognitive statin side effects was anecdotal, not supported by references, and had an excessive number of first person sentences. Even though most of the above authors, as well as Zoe Harcombe, Luca Mascitelli, Mark Goldstein, Uffe Ravnskov and I repeatedly responded to peer review criticisms and suggestions, our

revisions were rejected.

The editor explained that she had to abide by the peer review decisions and was obligated to notify the authors of the three satisfactory papers that these could be published in their regular March 2015 issue. She asked if I had any objection to this, since it would no longer have a special focus edition dedicated to Uffe as we had previously agreed. I saw no reason to refuse this request, and these papers apparently attracted more media attention over the next month than this journal usually receives in a year. I was anxious to see the other papers published and an eBook appeared to be the most rapid and cost effective way to disseminate this information. Most required only minimal revisions to be updated and since there were no space limitations, additional authorities could be invited to participate in this tribute to Uffe. In addition, all income from this eBook will go to defray the expenses of maintaining and expanding the THINCS website. Uffe has funded and performed all these duties since its inception but no longer has the time to devote to this. Fortunately, Andy Harcombe of Columbus Publishing has graciously agreed to take on this additional responsibility.

Authors prefer journals, since books are not indexed in Medline, PubMed or Embase and two of the original group decided to take this route. However, books, and especially eBooks, are increasingly accessible on search engines. Many find that Google retrieves pertinent information more rapidly than a Medline search, and that it is often more comprehensive and up to date. This is especially true when abstracts and keywords are prominently displayed on web sites. We plan to post these on the THINCS and as many other web sites as possible, along with a copy of the Table of Contents and information on how to obtain the eBook book at a very nominal fee. Another advantage of this is that eBook chapters can be periodically updated to include important new information that is pertinent. The following chapter outlines his numerous contributions, including establishing THINCS, and may help explain why this book has been dedicated to Uffe Ravnskov, MD, PhD.

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Chapter Two

On The Origin And Evolution Of THINCS

An interview with Uffe Ravnskov, MD, PhD

Paul J. Rosch, MD

As noted in my Preface, many scientist and physicians, including eminent authorities, have criticized the lipid hypothesis of coronary heart disease. Dr. George Mann, an early Co-Director of the Framingham Study and Professor of Medicine and Biochemistry at Vanderbilt University called it “the greatest scientific deception of this century, perhaps of any century.” However, nobody has done more to expose the flaws and dangers of this scam than Uffe Ravnskov, MD, PhD, and members of THINCS (The International Network of Cholesterol Skeptics), an organization he created in 2001. What is particularly noteworthy is that he had no particular background or expertise in nutrition or cholesterol metabolism when he began his investigations and has personally funded this campaign for the past 15 years. I was curious as to why he embarked on this and since I thought this might also be of interest to others, decided to explore this further in the following interview.

PJR: My recollection is it was shortly after receiving your MD from the University of Copenhagen in 1961 that you first became aware of the cholesterol theory of atherosclerosis. You subsequently developed an interest in Internal Medicine and Nephrology, obtained a PhD from the University of Lund in 1973, and entered into private practice in 1980. What was it that made you dispute the role of cholesterol and saturated fat in the pathogenesis of heart disease?

UR: You are right that I heard about the cholesterol hypothesis already in 1961, but I was confident that more wise researchers should show that this idea was without any evidence. Unfortunately I was wrong, but it took more

than 25 years before I started my research about this issue. I wanted to become a general practitioner, and I therefore started by working on various types of clinics in Denmark and Sweden in the sixties. At the medical department of a small country hospital in Sandviken, Sweden, two of our patients suffered from postmyocardial infarction syndrome (PMIS), which at that time was treated with cortisone. Both of them died later on, and at the autopsy I found that both of them had a small aneurysm of the heart. I was convinced that two rare phenomena in the same patient couldn't be an accident, and when I sought the literature in the nearby University library I found about a dozen case reports of PMIS. Most of the authors noted in passing the presence of a heart aneurysm, but nothing was mentioned about it in the discussion sections or in the abstracts. Therefore I wrote a paper, where I referred to these papers and warned against treating PMIS with cortisone, because I thought this was what had caused the aneurysm.¹

I was proud as a pope having published a scientific paper from a small hospital without assistance from my superior. I asked myself if I should devote myself to research instead. About the same time I treated a patient with acute renal failure with peritoneal dialysis, a new method at that time. That the patient survived and regained normal renal function started my interest in nephrology, and half a year later I obtained a temporary job in the Department of Nephrology at the University Hospital in Lund.

The academic level was not impressive in that department, so after some time I moved to the Department of Clinical Chemistry. Assisted by my supervisor Bengt G. Johansson, who was an expert in immune electrophoresis, I published several papers about proteinuria and introduced the albumin/creatinine clearance ratio as a more exact way to measure degree of albuminuria.²

When the professor at the nephrologic department retired, I went back. At that time Stephen Zimmerman and his co-workers had published a study of patients with glomerulonephritis (GN) and chronic renal failure, which showed that most of them had been exposed to toxic chemicals, most often hydrocarbons.³ I became curious, because it is well known that hydrocarbons are tubulotoxic, and in my previous studies I had shown that low-molecular-weight (LMW) proteins are filtered by the glomeruli and reabsorbed by the tubules, and also that in GN there was a strong, inverse

association between LMW proteinuria and glomerular function.^{4,5} I realized that tubular damage must be an important factor when renal failure appears in patients with GN.

My first publication in this area was a study of 15 patients with acute poststreptococcal GN. Ten of them had been exposed to organic solvents, either regularly on their work or acutely between the tonsillitis and the start of the GN. One year later renal failure was only present among those who had continued their exposure. I also interviewed 15 patients of the same age and sex, who had had an infection with the same streptococcal type without developing a GN. None of them had an occupation with exposure to solvents or had been exposed during the infection.

My finding was of course highly controversial because all experts “knew” (and still “know”) that GN is caused by immunologic damage of the glomeruli, and whereas all my previous papers had been accepted directly, this paper, which I sent to a kidney journal, was rejected after six months without any comments. A referee on *Acta Medica Scandinavica* rejected it as well, but after having corresponded with the editor, it became accepted.⁶

I organized a research group that included experts from Lund, Malmö and Copenhagen in medicine, immunology, pathology and occupational medicine. Occupational hygienists interviewed 150 patients with glomerulonephritis and we got a similar result as that of Zimmerman et al. and our lengthy report was accepted for publication in the *Quarterly Journal of Medicine*. But a serious problem occurred.

Two years before we submitted the paper I discovered that one of my clinical co-workers had falsified a paper, which was going to be included in his doctoral thesis. I tried to stop his dissertation by criticizing it in public, but in vain.

PJR: Why did you do it in public?

UR: Because of my bad manners. As a child I was never told how to behave. My mother wasn't interested in her children, and my father, who rarely was at home, died when I was 8 year old, so I had to learn everything by myself. Perhaps it also explains my disrespect for authorities. What I hadn't learned at that time was, that whistleblowers are not welcome in the

academic world.

Shortly afterwards the new professor arrived to our department. She was a good friend with the supervisor of my fraudulent colleague and had cooperated with him for many years previously at the university hospital in Gothenburg. When we had submitted our report, she found some careless mistakes in the text. I asked *QJM* to wait with the publication until we had corrected the errors, but this was not enough. Although the corrections had no influence on the results, the professor accused me for fraud and asked me to leave the department. If not, she would downgrade me and prohibit my research. I found it intolerable and opened therefore a private praxis in Lund in 1980.

PJR: Why didn't you seek employment at another university?

UR: Because she had told most of the Scandinavian professors in nephrology that I was fraudulent. However, I continued my research in nephrology. Totally I succeeded in publishing 20 papers about glomerulonephritis as a private practitioner. What I found was that glomerulonephritis is just as innocent as flu, unless the patient is exposed to tubulotoxic chemicals or drugs. However, according to the general view renal failure in GN is caused by immunological processes in the glomeruli, because numerous animal experiments have succeeded in producing GN with renal failure by injections of various microorganisms or other immunoreactants. What nobody seem to have understood is, that it cannot be produced unless the antigens are mixed with Freund's adjuvant, a tubulotoxic oil mixture, that is able to produce GN by itself.

One of my papers was published in *The Lancet* in cooperation with a statistician and Åke Nordén, professor in general medicine in Lund. We had compared the number of occupations where exposure to organic solvents was unavoidable or likely in the general population and among our patients with GN, and found that it was much more common among the latter.⁷ You can read a review of my research about GN on www.ravnskov.nu/GN.

Shortly after the publication of our *Lancet* paper, the subeditor David Sharp told me that my professor had sent a letter in which she claimed that all my papers about GN were fraudulent. I suggested him to ask her about the evidence. He had already done that, but as she had refused, her letter

was rejected. Instead she published it in *Acta Medica Scandinavica*, whose editor was a good friend of her. Therefore I asked David Sharp to publish it in *The Lancet* as well together with a short answer from me.⁸ I also sent my answer to *Acta Medica Scandinavica*, but whereas her letter was presented with a marked heading; my answer was published half a year later with no heading at all.

PJR: Didn't you react in some way?

UR: Yes of course. I contacted the dean of the medical faculty in Lund and asked him to let neutral experts analyze her accusations. Instead he asked the professor to select two researchers herself and she chose of course two friends of her. One of them was professor in psychology; the other one in nephrology but without any experience about glomerulonephritis or occupational medicine. I sent the dean a protest, but he didn't respond.

Without giving me an opportunity to respond, their first report was sent to a large number of colleagues including the head of the university, who immediately sent a letter back to all of them that he would retract my docent title (assistant professor). However, it was easy for me to show that their criticism was unfounded. A few weeks afterwards the dean and the vice dean came to my practice with many excuses and I kept my docent title as well. What I should have done was of course to sue her for slander, because she had sent her accusations to a large number of international colleagues as well, but at that time I didn't know that.

Another issue of my research was urinary tract infection. I tried for several years to tell Swedish doctors that a lower urinary tract infection in women is an innocent disease, which never result in renal failure, unless the patient has malformations or other defects of the urinary tract, and that more than 50 studies had shown that it could be cured by only three days treatment and even by a single dose of an antibiotic.⁹ At that time everybody "knew" that a urinary infection might progress to pyelonephritis and renal failure. Consequently many patients were prescribed antibiotics to use for several months or years.

One of my own observations as a practitioner was, that the main cause of dysuria is soap, not bacteria. Among 31 of my female patients with dysuria, 29 used soap to wash their sexual organs, whereas among 19 women with

asymptomatic bacteriuria 13 never used soap and four used it only once a week. I have never got such a strong statistical confirmation in my research – the p-value was <0.000001 .¹⁰

PJR: How did you become interested in the cholesterol hypothesis?

UR: When the cholesterol campaign started in Sweden in the eighties I became much surprised. I had followed the literature about cholesterol superficially, but had never seen anything in support. I became curious. Were the cholesterol researchers just as unwilling to listen to critical voices?

Several researchers had already documented that the cholesterol hypothesis was without scientific support. According to George Mann the villains were the drug and vegetable oil industries, the American Heart Association and the National Institutes of Health. I met him when we organized a meeting in Finland together with several skeptical Scandinavian researchers. He told us that he had been a member of the Framingham research group, but he left it when he realized that they didn't publish results that contradicted the diet-heart idea.

When I started reading the scientific literature about cholesterol I realized that most of the authors were just as blindfolded as those in the area of GN. I have learned that it is easy to publish correctly performed studies as long as they are in line with the accepted dogmas, but it becomes very difficult if they aren't. Consequently most of my papers about GN have been published in non-nephrological journals and I experienced that the same rules were present in the cholesterol field. When I sent a review where I pointed to the many contradictory findings, it was rejected by half a dozen medical journals before it was accepted in *Medical Hypotheses*.¹¹

What I also discovered was that many authors who hail the cholesterol hypothesis deliberately mislead their readers. To demonstrate it I checked how the authors of three, major authoritative reviews had referred to the literature. I was shocked. To cite part of the abstract of a paper I published about that issue:

“Only two of twelve groups of controversial papers were quoted correctly, and only in one of the reviews. About half of the papers were ignored. The rest were quoted irrelevantly; or insignificant findings in favour of the hypothesis were inflated; or unsupportive results were quoted as if they were

supportive. Only one of six randomized cholesterol-lowering trials with a negative outcome were cited and only in one of the reviews. In contrast, each review cited two, four, and six non-randomized trials with a positive outcome, respectively.”¹²

I have experienced the fraudulent methods used by the cholesterol fanatics more closely myself. In 1993 The National Food Agency in Sweden organized a conference about prevention of cardiovascular disease. I participated together with three cholesterol-critics; one of them was Lars Werkö, head of SBU (the Swedish Agency for Health Technology Assessment and Assessment of Social Services). The other participants were about 40 Scandinavian and British “experts”. They used a meta-analysis by the Norwegian statistician Ingar Holme¹³ as their main argument for their warnings against saturated fat. I had just published a meta-analysis of all the correctly performed cholesterol-lowering trials in *British Medical Journal*, where I showed that taken together, no benefit was achieved; in fact, total mortality was higher in the treatment groups.¹⁴ I had also included a table of the previous meta-analyses. One of them was the analysis by Holme, and in that paper he had excluded seven trials: most of them with a negative outcome, I wrote to him and asked why. I had also checked his data and found that there were numerous errors; most of them in favor of the diet-heart hypothesis. He admitted most of the errors and promised to correct them in his future publications. However, shortly afterwards he published two meta-analyses which included the same trials and with the same errors.^{15,16} Since then he has been a statistical coauthor of more than 40 statin trials.

PJR: You have published several critical books as well. How did you succeed with that?

UR: There were no major problems in the start. My first book was published in 1991 in Swedish and a year later in Finnish. Initially, there was much interest about it in the Scandinavian media. However, when Finnish television aired an interview with me, Finnish researchers critical to my view were asked to comment what I had said without informing me, and at the end of the program, my book was put on fire.

PJR: But as I remember it became much more difficult during the

following years

UR: Yes, after the introduction of the statins almost all of my papers were routinely rejected by U.S. and U.K. journals even though all my claims were supported by references to peer reviewed publications.

Later on I was interviewed by the Dutch TV-program Tros Radar. Soon afterwards the leading cholesterol experts in Holland described me in another Dutch TV program as a crackpot, who had been expelled from the universities of Copenhagen and Lund, and that my only contribution to science was a letter, which I had published in 70 different publications. However, the head of Tros Radar called the universities, and when she realized that the experts had lied, she invited them to debate with me on a follow-up program, but they declined: To discuss with a maverick who claims that the earth is flat would be a tremendous waste of time.

PJR: But what about your books?

UR: For several years I tried to find a book agent or a publisher for the English version of my book, but no one was interested. Therefore, I published parts of it on the web. This soon became one of the top ten sites for searches on cholesterol at that time, and I began to receive numerous e-mails from doctors, scientists, patients and journalists who supported my views.

One of them was Mary Enig, a biochemist who for many years had tried to inform the world about the dangerous effects of trans fat. She introduced me to Sally Fallon, president of Weston A. Price Foundation, who published my first book in English, *The Cholesterol Myths; the Fallacy that Saturated Fat and Cholesterol cause Heart Disease*. She also invited me and my wife Bodil to Washington, where she had arranged several talks and radio interviews.

PJR: Please tell me what led to your organization of THINCS. I had long been critical of the lipid hypothesis and devoted several sessions to exposing its flaws at our annual International Congress on Stress in Switzerland starting in 1993. These included presentations by George Mann, Bill Stehbens, “Pete” Ahrens, Ray Rosenman, Stewart Wolf and other authorities, but I was unaware of your contributions. I learned about them from Ray Rosenman, a close friend and Vice President of The

American Institute, who urged me to join THINCS, which I did in early 2003. I first met you several months later at the May 2003 annual Weston Price Conference in Virginia, where I was invited to give a presentation titled “Cholesterol Does Not Cause Coronary Heart Disease and Statins Don’t Work by Lowering Lipids: The Role of Inflammation and Stress.

By that time there were about 50 members of THINCS, some of whom also participated, including Kilmer McCully (Homocysteine, Vitamins and Vascular Disease), Peter Langsjoen (CoQ10 Depletion From Statins), Leslie Klevay (Copper Deficiency and Coronary Disease) and your talk (High Cholesterol May Protect Against Infections And Atherosclerosis). I had become aware of Duane Graveline’s experience, and arranged for his presentation (Transient Global Amnesia – A Side Effect of Statin Treatment) and he quickly joined our group. Eddie Vos, a mechanical engineer and THINCS member also participated, and there may have been others that I did not meet. I was impressed with the quality of these papers as well as their diversity and continue to be astounded by the contributions of subsequent THINCS members, which now exceed one hundred.

UR: To fight alone is not a good idea; in particular if you are working alone as a private practitioner. As you mention, my book and my websites had resulted in several interesting contacts with wise colleagues, who were just as critical to the cholesterol campaign as myself.

Among the members present at the Weston A. Price meeting I would also like to mention the Polish-Australian pharmacologist and toxicologist Bogdan Sikorski. Bogdan worked at TGA, the Australian equivalent to FDA, and according to a recent investigation they had found that about half of all clinical studies and trials were fraudulent. He told me about Jan Kwasniewski, the Polish doctor, who already in the sixties introduced “the optimal diet” in Poland. This was an extreme LCHF diet, by which he said that he had cured many patients from multiple diseases, for instance MS, ALS, Crohn’s disease and type 1 and type 2 diabetes. I asked Bogdan, why he hadn’t published his findings. Bogdan had asked him the same question. His response was that “No one wants to know!”

One of the early members was Dag Viljen Poleszynski, a Norwegian professor with several academic titles, author of more than 30 popular-scientific books and editor of a magazine about alternative medicine. A few

years later Kaare Norum, one of the leading cholesterol fanatics in Norway succeeded in expelling him from the high-school because of his skepticism against the cholesterol campaign.

Many more interesting individuals contacted me, and it gave me the idea to start an electronic network of university people skeptic to the cholesterol hypothesis and the diet-heart idea. At the start our organization included about 40 members with varying backgrounds and hypotheses about the cause of atherosclerosis and cardiovascular disease, but with skepticism as a common denominator. Since then we have had many interesting discussions on the web.

PJR: We next met in 2008 in Gothenburg, where you were the recipient of the Leo-Huss-Walin Prize for independent thinking. I had been invited to give the opening lecture at the Award ceremony, and other THINCS members who presented included Michel de Lorgeril, Peter Langsjoen and yourself. Professors Richard Feinman, Tore Scherstén and Björn Folkow, who were not THINCS members also spoke, and it appeared from the discussion period that most of the audience supported our opinions but were not aware of THINCS. I have been impressed with the large number of other qualified physicians and scientists who share our views, but have not joined THINCS, which does not require any membership fees or other costs. I believe their ranks are increasing and wondered what your experience has been in this regard.

UR: It is very difficult for medical researchers to go against the common view. Almost all research about atherosclerosis and cardiovascular disease is funded by drug companies, and they are generous. Therefore, researchers, who appear on our members list, would immediately lose their financial support and also support and respect from their colleagues. As you know, a paradigm shift in medical science may not happen before most of the leading professors have retired or died.

PJR: This is reminiscent of Max Planck's observation that "*A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.*" You referred earlier to the difficulty in getting anything published in a peer reviewed journal that was critical of the

cholesterol hypothesis or the efficacy and safety of statins. As a result, many frustrated researchers and other have resorted to writing books. Although these are not accessible via Medline, Embase etc., some have become best sellers in their field. The Cholesterol Myths has been out of print for some time, but apparently is available on line at no charge. What prompted you to write *Fat and Cholesterol are GOOD for You!* and *Ignore the Awkward*.

UR: I had been told that many lay people found that The Cholesterol Myths is not too easy to read. Furthermore, due to a different view on the cause of atherosclerosis, Sally Fallon stopped publishing it. To find a new publisher would demand much work, and I therefore allowed it for free. Instead I wrote a shorter and more popular-scientific version. I also found it interesting to tell about the many ways we are fooled by the drug industry and their paid scientist, which was my motive for writing *Fat and Cholesterol Are Good for You*. However, I have not yet succeeded in publishing a best seller.

PJR: One of the problems is of course that few medical journalists dare to write about the many contradictions to the cholesterol hypothesis.

UR: You are right. I can give you an example. In 2006 I was invited to a conference in London, where supporters and opponents to the cholesterol hypothesis were asked to present their arguments to a large number of British journalists. At the start they were asked whether they were believers or not, and almost all of them voted as believers. At the end of the conference they were asked again, and almost all of them had changed their mind. I was confident that now the journalists should start writing critical articles, but I was wrong – not a single one appeared after our meeting.

PJR: Tell me about the hypothesis about atherosclerosis, which you have presented together with Kilmer McCully.

UR: By reading systematically about the lipoproteins I had learnt, that they participate in the immune system by adhering to and inactivating all kinds of microorganisms. As this fact, documented by more than a dozen research groups was unknown for most researchers I published a review about it.¹⁷ Among the opponents at the meeting with the journalists was our member

Malcolm Kendrick. When I listened to his description of the vulnerable plaque, it struck me how it was created; it might simply be a microscopic boil, which starts the formation of an arterial thrombus, when it ruptures. During the following year I used most of my time to formulate my idea in more detail, but my final manuscript was rejected by nine journals. Here are their responses:

August 3, 2007. *Nature*: “We must decline it on editorial grounds. ”

August 5, *Nature Medicine*: “We feel the work is better suited for a journal specialized in cardiovascular disease. ”

August 8, *The Lancet*: “It would be better placed elsewhere. ”

August 20, *Science*: “Although your analysis is interesting, we feel that the scope and focus of your paper make it more appropriate for a more specialized journal. ”

September 19, *Journal of Infectious Diseases*: “The manuscript is better suited for a different journal. ”

March 17, 2008, *Clinical Science*: “Your proposal appears to be more suited to a medical hypothesis journal.”

March 26, *Journal of Clinical Investigation*: “We feel the manuscript would not be appropriate for publication in the Journal of Clinical Investigation.”

March 31, *Archives of Pathology*: “Unfortunately, your manuscript is not consistent with our current priorities for publication in the Archives.”

April 15, *Archives of Internal Medicine*: “After some effort, we have been unable to identify a qualified author for an opposing paper. ”

A little later I discussed my hypothesis with Kilmer McCully. He bought it immediately because his own hypothesis about homocysteine fits perfectly into mine. He added some sections about the role of homocysteine and as he is a coeditor of *Annals of Clinical and Laboratory Science*, they accepted our paper directly.¹⁸

PJR: But there were no problems associated with our cancer paper.¹⁹ How

come?

UR: A paper written by a retired private doctor outside the academic world is less attractive for editors of a medical journal than a paper authored by one or more professors. I think that my two famous coauthors made our paper more acceptable.

PJR: But although we have presented massive evidence in support of the idea that low cholesterol predisposes to cancer, supporters of statin treatment claim that the statins are protective.

UR: Evidently they haven't read our paper, or they do it on purpose by economical reasons. Their evidence is cohort studies where statin-treated people are compared with untreated. Obviously those on statin treatment may have lived most of their life with high cholesterol and it is well known that many statin-treated patients stop their treatment. As high cholesterol is associated with a lower risk of cancer, this can explain the lower number of cancer, in particular because most of the untreated controls may have lived most of their life with normal or low cholesterol. It is also curious, that none of the authors of these studies have any comments to the fact that several statin trials have resulted in a significant increase of cancer in the treatment groups and the fact that statins are carcinogenic in rodents.

PJR: What do you think about the future? Is it possible to stop this madness in a foreseeable coming?

UR: A difficult question, indeed. Almost 60 years ago Fred Kummerow, previously professor of comparative biosciences and one of our members, described the dangers associated with eating partially hydrogenated oils (trans fatty acids), which has been a major component in many types of margarine for almost hundred years.²⁰ In 2013 he filed a lawsuit against the FDA, which had ignored his petition sent four years previously calling for ban on artificial trans fats. Two years later FDA reacted and forbid food containing such fats, but they gave the manufacturers a deadline of three years.

Fred succeeded, but to win, you obviously have to become a centenarian, like Fred. He is still active; for instance you can read about his experience

in this field published last year in World Nutrition,²¹ and he was also a coauthor to a paper that we published recently in Mayo Clinic Proceedings.²²

PJR: Thus it took almost 60 years for Fred. Do you think the same is valid for you?

UR: Hopefully not. I think that William Stehbens, one of our early members, was the first who questioned the cholesterol hypothesis and it was more than 40 years ago,²³ but when Joseph Goldstein and Michael Brown received the Nobel Prize in 1985, everybody became convinced about the role of high cholesterol. But what Goldstein and Brown showed was, that the cellular LDL-receptors of people with familial hypercholesterolemia were less effective as in normal people, not that high cholesterol is the cause of atherosclerosis or coronary heart disease. Since then several of our members have documented, both in medical journals, books and newspapers, that high cholesterol and saturated fat are our good friends. If you search PubMed and Google with the names (in alphabetic order) Michel de Lorgeril, Mary Enig, Duane Graveline, Zoë Harcombe, Malcolm Kendrick, Lesley Klevay, Louis Krut, Peter Langsjoen, Luca Mascitelli, Kilmer McCully, Harumi Okuyama, Ray Rosenman, Stephanie Seneff, Morley Sutter, Jørgen Vesti Nielsen, Eddie Vos, Glyn Wainwright and our own, the list of references would fill many pages.

However, it is not an easy task to question Nobel Prize winners. My first paper questioning their idea was published 36 years ago,²⁴ but it made no impact whatsoever. I also sent a kind letter to both of them pointing at the many findings that contradicted their idea, but they never answered. Our recent paper, where we have documented that people above the age of 60 with high LDL-C live the longest,²⁵ should hopefully open the eyes of many scientists, but I doubt that it is able to stop the cholesterol madness; there is too much money involved. It took almost 60 years for Fred Kummerow to change the view about trans fat; we have only tried for 40. As the great artist Freddie Mercury sang: “The Show Must Go on.”

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Chapter Three

How Dietary Guidelines, Bad Science, Politics And Profit Have Contributed To The Current Epidemic of Obesity and Incidence of Heart Disease

Zoë Harcombe, PhD

Abstract

In 1960, 13.3% of United States (US) adults were obese; 44.8% were overweight.^{1a} Age adjusted all-cause mortality was 1,339.2 per 100,000 population, a death rate of 1.33%.^{2a} “Diseases of heart” mortality was 559.0 per 100,000 population, a death rate of 0.56%.^{2b}

By 2007, 34.7% of US adults were obese; 67.7% were overweight.^{1b} Age adjusted all-cause mortality was 760.2 per 100,000 population, a death rate of 0.76%.^{2c} Heart disease mortality was 190.9 per 100,000 population, a death rate of 0.19%.^{2d}

Heart deaths accounted for 42% of all deaths in 1960 and 25% of all deaths in 2007. Smoking more than halved during this period from 41.9% of US adults in 1965 to 19.7% in 2007.³

In fewer than five decades we have witnessed an obesity problem become an epidemic and failed to reduce heart disease by more than smoking cessation and advances in medical care facilitated. This paper argues that this scenario is of our making.

Diet-heart hypothesis

What has become known as the diet-heart hypothesis has its origins in the works of Russian pathologists at the turn of the twentieth century. Pre World War I, the works of Ignatowski,^{4,5,6} Stuckey,^{7,8,9} Chalатов,¹⁰ Wesselkin¹¹ and Anitschkow¹² established associations between dietary interventions and fatty deposits/thickening of the intima in rabbits. The

dietary interventions involved administering foods of animal origin, as sources of cholesterol and fat, to herbivorous rabbits. Knack questioned the validity of this and discovered that rabbits fed a plant diet with added cholesterol showed no arterial damage while rabbits fed eggs and milk, substances that they cannot digest, did.¹³ Anitschkow tested omnivorous rats and found egg yolk administered in milk produced no observable changes in the aortas.¹⁴ Regrettably the herbivore limitations were ignored and the hypothesis of an association between cholesterol in food and indications of heart disease gathered momentum.

In the 1950s, Ancel Keys comprehensively tested the hypothesis that dietary cholesterol increased serum cholesterol levels.^{15a} Keys concluded that “The evidence - both from experiments and from field surveys - indicates that cholesterol content, *per se*, of all natural diets has *no* significant effect on either the cholesterol level or the development of atherosclerosis in man.”¹⁶

The erroneous notion that dietary cholesterol can increase serum cholesterol prevails with modern dietary advice to avoid egg yolks and seafood specifically and animal foods generally.

Having determined that dietary cholesterol has no significant effect on either the cholesterol level or the development of atherosclerosis in man, Keys maintained the view that diet and serum cholesterol levels were significant determinants of heart disease. At the Mount Sinai symposium, Keys presented a now well-known graph, showing an association between deaths from heart disease per 1,000 US men aged 55-59 and fat calories as a percentage of total dietary intake.¹⁷ Criticisms were made that data were available for 22 countries, showing a scatter plot, rather than a linear relationship.¹⁸ By the time this 1957 retort had been published, the Seven Countries Study had been conceived, planned and was underway.

The Seven Countries Study noted that “Epidemiological studies alone can rarely if ever produce final proof of a causal sequence.”^{19a} Despite acknowledgment of this limitation, positioning the Coronary Heart Disease (CHD) death rate as 42% (of deaths), as opposed to 0.56% (of people), created a sense of urgency: “The urgency of finding means of prevention is sharpest for men in middle age ... Starting with men aged 40 through 59, the follow-up would show CHD causing close to 40% of all deaths in five

years.”^{19b}

The introduction to the Seven Countries Study was not explicit about the study hypothesis.^{19c} The opening chapter stated “By the mid-1950’s epidemiological studies had identified two important risk factors in the development of CHD among middle-aged white men in the United States.” These risk factors were not stated, but Keys’ view that dietary fat and serum cholesterol levels were the prime risk factors were so strongly held at this time, he may have assumed that they did not need clarification.²⁰

The Seven Countries study examined 12,770 men, aged 40 through 59 years, in 16 cohorts in Finland, Greece, Italy, Japan, the Netherlands, the United States, and Yugoslavia from 1956 onwards. As the study progressed, dietary fat generally became saturated fat specifically although Keys was unscientifically casual in his use of these terms. The verbatim conclusions were:

- “The incidence rate of CHD tends to be directly related to the distributions of serum cholesterol values.”
- “The average serum cholesterol values of the cohorts tended to be directly related to the average proportion of calories provided by saturated fats in the diet.”
- “The CHD incidence rates of the cohorts are just as closely related to the dietary saturated fatty acids as to the serum cholesterol level.”²¹

The diet-heart hypothesis thus became the tripartite association of saturated fat, serum cholesterol levels and CHD.

Bad Science

The administration and conclusions of the Seven Countries Study made a number of nutritional errors:

1) Animal foods had been exonerated

The only foods that contain dietary cholesterol are of animal origin: meat; fish; eggs and dairy products. Having extensively tested high cholesterol

diets with human subjects, with the conclusion that these had no significant impact on serum cholesterol levels or the development of atherosclerosis in man, it follows that animal foods *per se* have no significant impact on serum cholesterol levels or the development of atherosclerosis in man.^{15b}

All foods, except sucrose and oils, contain protein. Meat and fish are combinations of water, fat and protein. Glycogen in offal aside, meat and fish are void of carbohydrate. Dairy products contain some carbohydrate and eggs have a trace. The macronutrient entirely, or largely, absent in animal foods is carbohydrate. Plant foods are primarily combinations of water, carbohydrate and protein. The macronutrient largely absent in plant foods is fat, although most foods of vegetable origin, from blueberries to oats, have trace to small amounts. The exceptions to these principles are nuts and seeds, containing all three macronutrients in good measure.

Having exonerated animal foods in his human dietary cholesterol studies, the obvious macronutrient for Keys to have studied was carbohydrate, not fat.

2) Carbohydrates were misclassified as fats

Keys did in fact study carbohydrate, but incorrectly classified substances such as cake and ice cream as fat. They contain fat, but are predominantly carbohydrate.^{22a}

In the most comprehensive write up of the Study, “Seven Countries: a multivariate analysis of death and coronary heart disease”, Keys noted: “The fact that the incidence of coronary heart disease was significantly correlated with the average percentage of calories from sucrose in the diets is explained by the inter correlation of sucrose with saturated fat.”²³

Sucrose and fat do not occur naturally together in food; avocado being an exception. This admission thus confirmed i) that processed foods, such as cake and ice cream, were erroneously deemed fat and ii) that processed foods *per se* could be risk factors for heart disease, not any natural fats contained therein.

3) Fats were misclassified

A nutritional error of the time, which prevails today, was the assumption

that fats of animal origin are saturated and fats of plant origin are unsaturated. Every food that contains fat contains all three fats: saturated; monounsaturated and polyunsaturated. There are no exceptions.^{24a}

Volume VII of the Seven Countries study described rural Italy: “The cuisine of Bologna and Modena is the richest of the regional cuisines of Italy, it is loaded with saturated fatty acids and cholesterol from butter, cream, meats, and eggs.”²⁵ The mention of dietary cholesterol was unnecessary, having been declared to have no impact on serum cholesterol or the development of atherosclerosis in man. The assumption that meats and eggs are “loaded with saturated fatty acids” is incorrect. Sirloin steak, for example, is approximately 71% water, 21% protein, 3% unsaturated fat and 2% saturated fat (trace minerals and rounding error account for 100%).²⁶ Of the 10 g of fat per 100 g of egg, 37% is saturated, 46% is monounsaturated, and 17% is polyunsaturated.²⁷

In the rare dietary references in the Seven Countries Study, Keys complimented vegetable fats, such as olive oil, and denigrated animal fats, such as meat. Keys noted that the Yugoslavian cohort of Dalmatia consumed olive oil “to the exclusion of almost all other fat”, while in Slavonia “animal fat, especially pork fat, takes the place of oil in the diet.”²⁸ Keys did not demonstrate the nutritional knowledge that one tablespoon of olive oil²⁹ has more than three times the total fat and a third more saturated fat than a 100g pork chop.^{30a} Such nutritional ignorance continues to be widespread more than 30 years later.

The only food group that contains more saturated than unsaturated fat is dairy products.^{24b} Dairy products have many health benefits being rich in vitamins and minerals, especially the bone nutrients: calcium; vitamin D and phosphorus. The most recent meta-analysis of studies evaluating dairy products and health factors concluded: “The observational evidence does not support the hypothesis that dairy fat or high-fat dairy foods contribute to obesity or cardiometabolic risk.”^{30b}

Dietary Guidelines & Politics

US public health dietary advice was announced by the McGovern Select Committee on Nutrition and Human needs in 1977^{31a} and was followed by

UK public health dietary advice issued by the National Advisory Committee on Nutritional Education in 1983.^{32a} Dietary recommendations in both cases focused on reducing dietary fat intake; specifically to i) reduce overall fat consumption to 30% of total energy intake and ii) reduce saturated fat consumption to 10% of total energy intake.

The UK nutritional guidelines^{32b} made reference to the Seven Countries Study, the US committee document^{31b} did not. There were five Randomized Control Trials (RCTs), examining dietary fat interventions, all-cause mortality and CHD mortality, available to the US committee^{33a,34,35,36,37} and a sixth was available to the UK review group.^{38a} None of these RCTs were referenced by either dietary committee. The US Committee publication reported data from the non-randomized, cross-over trial, the Finnish Mental Hospital Study.^{39a,40a}

None of the five RCTs tested the dietary fat recommendations introduced. The sixth, Woodhill,^{38b} tested the 10% saturated fat recommendation and reported significantly more deaths in the intervention group. The six RCTs, combined in meta-analysis, reported no difference in all-cause mortality and no significant difference in CHD mortality.⁴¹

The UK Committee on Medical Aspects of Food Policy admitted: “There has been no controlled clinical trial of the effect of decreasing dietary intake of saturated fatty acids on the incidence of coronary heart disease nor is it likely that such a trial will be undertaken.”^{42a}

This was reiterated by Truswell in his 1994 review of the data: “It has been accepted by experienced coronary disease researchers that the perfect controlled dietary trial for prevention of coronary heart disease has not yet been done and we are unlikely ever to see it done.”^{43a}

It was confirmed again by the UK Food Standards Agency in 2009: “The ideal controlled dietary trial for prevention of heart disease has not yet been done and it is unlikely ever to be done.”⁴⁴

These facts are not widely known. US and UK citizens believe that government dietary recommendations have been proven; they have not been tested.

The Seven Countries Study disregarded the totality of country data available. It selected countries, which the Mount Sinai presentation showed would concur with a fat-heart hypothesis. It could at best show association

and failed to establish this in five cohorts: West Finland; Rome; Crete; Belgrade and Corfu.^{45a} It made several nutritional errors about dietary fat, cholesterol and carbohydrate and misclassified foods as a result.

Randomized Controlled Trials were not taken into account and they would not have supported the introduced dietary guidelines had they been. Evidence and interviews of the time confirm that the dietary guidelines were political rather than evidential.⁴⁶

Dietary Guidelines and food intake

The primary nutritional impact of dietary recommendations to decrease fat was that carbohydrate intake concomitantly increased. With protein in all foods, with the two exceptions noted, advice to decrease fat/protein necessarily increases carbohydrate/protein, as a proportion of dietary intake, if not as an absolute amount. US dietary guidelines reinforced this inevitable consequence: “Increase carbohydrate consumption to account for 55 to 60 percent of the energy (caloric) intake.”⁴⁷ The UK publication positioned the carbohydrate recommendation as an opportunity emanating from the fat advice: “The panel sees advantages in compensating for a reduced fat intake with increased fibre-rich carbohydrates (e.g. bread, cereals, fruit and vegetables).”^{42b}

A United States Department of Agriculture review of dietary recommendations throughout history compared the “Basic four foundation advice” of 1956-70s with the 1984 Food Pyramid guide, which followed the McGovern committee guidelines.⁴⁸ The basic four advice was based on four food groups: meat; milk; bread and cereals; fruits and vegetables. Four portions a day of starchy carbohydrates, such as bread and cereal, were recommended (a slice of bread was given as an example portion). The Food Pyramid named six food groups: dairy products; meat, poultry, fish, eggs, beans and nuts; breads, cereals, rice and pasta; vegetables; fruits; and fats, oils and sweets. Recommended servings of starchy carbohydrates increased to 6-11 daily (a slice of bread remained the example portion size). Fruit servings of 2-4 per day were recommended and sweets were inexplicably featured in the fats and oils food group, thus adding significant amounts of sucrose to starch intake. The addition of recommendations for 3-5 servings

of vegetables brought Tanner's obesity advice of 1869 to mind: "Farinaceous and vegetable foods are fattening, and saccharine matters are especially so."⁴⁹

The *Dietary Guidelines for Americans* are issued every five years. Table 2.2 in the most recent edition, 2010, reported dietary intakes for American adults.^{50a} The main source of calories was grain-based desserts (cakes, cookies, pies, cobblers, sweet rolls, pastries and donuts). Yeast breads (including bagels and rolls, white, whole-wheat and multi-grain) were in second place. Chicken dishes (dominated by take-away fried chicken and chicken nuggets, rather than home-cooked grilled chicken) were in third place. The fourth highest source of calories for US adults was the soda/energy/sports drinks category and alcohol was in fifth place.

The American diet is dominated by processed food. The top 25 sources of calories contained only one listing of natural food: "regular cheese". The milk line entry was reduced fat and thus adulterated: fat, taste, satiety and nutrients having been removed. There were mentions of other real foods, such as fish, eggs and beef, but such categories included processed variants, for example: breaded fish; quiche; and beef noodles.^{50b}

Analysis of Table 2.2 revealed that carbohydrate based items accounted for 67% of the calorie intake from the most consumed 25 foods and 50% of total adult caloric intake. The carbohydrates were typically the starches recommended in dietary guidelines: bread; cereals; potatoes; rice; and pasta.^{50c} US Department of Health data confirmed that carbohydrate accounted for approximately 50% of the American adult diet; fat contributed 34% and protein made up the remaining 16% and that this had remained stable this (twenty-first) century.⁵¹ Saturated fat intake was 11%. American diets were 4% higher in fat and accordingly lower in carbohydrate than government recommendations, but the dietary guidelines were mostly being achieved.

The primary benefactors of the dietary guidelines were the cereal and grain producers. "[Annual] Per capita use of flour and cereal products reached 200 pounds in 2000 from 138 pounds in the 1970s".⁵² Annual per capita intake of sweeteners increased from 123.7lb in the 1970s to 152.4lb in 2000. High fructose corn syrup, Corn Syrup (HFCS) consumption increased almost twelve-fold from 5.5 to 63.8 annual pounds per capita.

Salad and vegetable oil intake almost doubled, while annual butter intake remained constant at a relatively insignificant 4.6lb per person. Whole milk consumption in 2000 was almost one third that of the 1970s. Consumption of low-fat milk almost doubled in parallel. Red meat and egg intake fell; white meat intake rose. It cannot be argued that butter, eggs, red meat and whole milk - foods that our grandparents would have relied upon - have caused the obesity epidemic. HFCS, vegetable oils and cereals are implicated.

Vegetable oil producers have also benefitted from the dietary guidelines. Reinforcing nutritional ignorance promoting plant fats as unsaturated and animal fats as saturated, traditional fats such as lard (60% unsaturated⁵³) have been rejected in favour of modern processed oils, less stable at cooking temperatures.⁵⁴ This switch has been supported by meta-analysis,⁵⁵ which included the discredited Finnish crossover trial^{39b,40b} and excluded the two RCTs with significantly more deaths in the diet interventions,^{33b,38c} and contained Aramark and Unilever declarations of interest. The Finnish crossover trial was excluded by Truswell^{43b} and the definitive Cochrane review,⁵⁶ as “inappropriate for assessing effects on cardiovascular events or mortality.” The study selection of the Mozaffarian meta-analysis has been questioned,⁵⁷ as has the safety of vegetable oils generally.⁵⁸

The misclassification of predominantly carbohydrate foods as saturated fats, made by Keys in 1970,^{22b} continued decades later. The *Dietary Guidelines for Americans* listed: ice cream; sherbet; frozen yogurt; cakes; cookies; quick breads; doughnuts; margarine; sausages; potato chips; corn chips; popcorn and yeast bread as major sources of saturated fats.⁵⁹

The Executive Summary of the *Dietary Guidelines for Americans* noted the “epidemic of overweight and obesity affecting men, women, and children in all segments of our society” making no connection with the rise in obesity since dietary guidelines were introduced. The introduction reported that 24 million Americans, almost 11% of the adult population, were diabetic and 78 million Americans, 35% of adults were pre-diabetic.^{50d} This has recently been updated to 29 million diabetics and 86 million pre-diabetics.⁶⁰ A recent review in *The Lancet*, estimated that the lifetime risk for developing diabetes was 40.2% for American men and 39.6% for women.⁶¹ Diabetes was correctly described as a condition of

high blood glucose levels and impaired glucose metabolism, but the connection between this epidemic, and advising Americans to base their meals on glucose, was not made.

The Executive Summary assumed that calories explain the obesity epidemic: “Americans must decrease the calories they consume and increase the calories they expend.” Calories do not explain the obesity epidemic. Notwithstanding that the calorie theory (one pound of fat is 3,500 calories and a deficit of 3,500 calories will elicit a loss of one pound of fat), which has become folk lore, has no evidence base or proof,^{45b} if it did hold it could not explain the data. Mean daily calorie intake for men was 2,450 in 1971-74 and 2,656 in 2005-2008.⁶² Mean daily calorie intake for women was 1,542 in 1971-74 and 1,811 in 2005-2008. The data represented an average increase of five calories per day, year on year, for men and approximately seven calories per day, year on year, over this period for women. If one additional jelly bean could create an obesity epidemic, as Taubes posited, the issue becomes how did we *not* have an obesity epidemic in the millennia since *Australopithecus Lucy*, not how did we since the 1970s.^{63a}

The calorie theory does not provide motive. It is the gluttony/sloth hypothesis. Researchers at the University of Florida discovered that formerly obese patients would prefer to be normal weight with a major disability (deaf, blind, one leg amputated) than morbidly obese.⁶⁴ Expenditure on diet products and services and preparedness to risk death with bariatric surgery,⁶⁵ further substantiates the motivation to avoid obesity. It is implausible that the human population maintained normal weight for approximately 3.5 million years and then chose to become greedy and lazy, to the point of epidemic, in a moment in evolutionary terms.

Profit & Food Politics

Natural food production is not lucrative. The ‘farm to fork’ logistics chain for steak, eggs or apples, is succinct and without opportunity or necessity for ‘added value’. Processed food production, and the marketing and advertising that accompanies it, is profitable for many contributors from

product concept to promotional toys.

The world's largest processed food and drink company, PepsiCo, had revenues of \$66.415 billion in 2013.⁶⁶ PepsiCo is the size of Sudan. It is bigger than 65% of the countries of the world.⁶⁷ PepsiCo is also a premier sponsor of the American Dietetic Association, which was renamed the Academy of Nutrition and Dietetics in 2012.^{68a}

Other premier sponsors of American Dietitians are: CoroWise, Cargill; General Mills; Kellogg Company; Mars Incorporated; McNeil Nutritionals; SoyJoy; Truvia sweetener and Unilever. The Academy has the following partners: Abbott Nutrition; Aramark; Coca-Cola; Hershey and the National Dairy Council.^{68b}

The Commission on Dietetic Registration (CDR) is the credentialing agency for the Academy of Nutrition and Dietetics. Its purpose is to ensure that registered dietitians alone are able to give food and nutrition advice. The CDR was formed in 1969. In 1984 the first registration eligibility reciprocity agreement was signed with the Canadian Dietetic Association. In 1991 registration eligibility reciprocity was extended to foreign countries whose goals were comparable to CDR's. In 1995 the CDR filed registration eligibility requirements and reciprocity agreements with the USA Trade Representative Office and World Trade Organization. By 2013, 89,385 dietitians were registered with the CDR.⁶⁹

47 of the 50 States of America have passed legislation to regulate who is able to provide nutritional advice through licensure, statutory certification or registration.^{70,71} The Commission on Dietetic Registration has successfully established a monopoly position for the Academy of Nutrition and Dietetics, which in turn is integrally partnered with the processed food industry. The fake food industry is embedded in our dietary advice; the real food message has no chance of success. Dietetic organisations from Australia to the UK are similarly conflicted.^{72,73,74}

What Does The Future Hold?

To the growing number of real food campaigners, the solution to the obesity and diabetes epidemics and incidence of heart disease is to return to eating the natural foods that we ate before we developed these epidemics.

Government food pyramids, plates and dietary guidelines should be torn up and replaced with one message: “Eat real food.” Children can and should be taught the difference between real and processed food (fields, not factories). They should reach adulthood knowing that grain-based desserts, yeast breads and chicken nuggets do not constitute a human diet. Banning trans fats and sweeteners, taxing sucrose punitively and any policy that facilitates consumption of real food should be embraced.

Humans need to remember the purpose of food. Food provides essential fats, amino acids, vitamins and minerals vital for survival. The optimal providers of these essential nutrients are natural foods, especially those of animal origin.^{24c} These are the foods that took us from Neanderthal to rocket scientist.⁷⁵ These are the foods we have been told to avoid.

The solution is so obvious that only an understanding of how we got to the current situation can explain why the solution will not be implemented. The erroneous demonization of fat generally and saturated fat particularly, without accurate definition of either term, has been reiterated by successive governments for decades. Admissions of error would harm reputations and could incur compensation claims. Additionally, dietary guidelines have been so lucrative to processed food manufacturers, and pharmaceutical companies treating the concomitant illness, that the resistance to change has been institutionalized. Nowhere more so than in America, with state legislation having granted food conglomerates monopoly access to unsuspecting consumers via dietitians.

The 2015 *Dietary Guidelines for Americans* will be virtually identical to those published in 2010, 2005, 2000, 1995, 1990, 1985 and 1980. The UK has no process for reviewing dietary guidelines and has no impetus to do so. There will be minor shifts in position by governments to distance themselves from advice so wrong that it can no longer be repeated. An example has occurred in the UK with the non-evidence-based five-a-day message having included fruit juice and then having limited fruit juice to one portion and more recently having announced that fruit juice is too sugary to recommend.⁷⁶ The processed food industry will also make token changes, especially where changes are to their benefit, for example: making smaller confectionery bars for the same price; replacing butter with cheaper vegetable oils.

The only significant change will emanate from the real food movement, which, facilitated by the internet and social media, is gathering momentum. Low carb high fat (LCHF) is being adopted by increasing numbers of individuals in direct contrast to the low fat high carb (LFHC) government dietary advice. Adoptees are losing weight, gaining health and managing type 2 diabetes with a diet primarily based on meat, fish, eggs and non-starchy vegetables.^{77,78} Sweden led the ‘underground’ trend towards LCHF and this has since been scientifically reviewed and endorsed by authorities.⁷⁹

The US and UK, having been the first to introduce high carbohydrate dietary advice will be the last to change. Their citizens will need to take their health into their own hands.

Peter Cleave was one of many doctors and researchers who testified at the McGovern dietary guidelines committee. Cleave argued: “*For a modern disease to be related to an old-fashioned food is one of the most ludicrous things I have ever heard in my life.*”^{63b} The committee did not find the concept of heart disease being related to natural foods ludicrous and we have had 35 years to experience the consequences.

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Chapter Four

The Culprit in Coronary Disease Is *Trans* Fats, Not Cholesterol: But Why Did It Take Decades to Ban Them?

Fred A. Kummerow, PhD

Abstract

Partially hydrogenated vegetable oils (PHOs) have been in the American diet since 1910. More than 50 years ago it was discovered that they contained *trans* fatty acids that were different from natural fatty acids in plant oils and in animal fat. There was growing evidence that the consumption of artificial *trans* fats had negative health effects, including increasing plasma lipid levels. In 2003, the Food and Drug Administration (FDA) ruled that the amount of trans fat in a food item must be stated on the label. In my opinion negative health effects can only be changed by banning artificial *trans* fats. A petition was filed with the FDA in 2009 to ban artificial *trans* fat and followed by a lawsuit in 2013. The decision to ban artificial trans fat was finally realized June 16, 2015. Some of the key issues that explain why it took so long to ban them include:

- Shortening produced from the partial hydrogenation of soybean oil was first thought to be a miracle fat because of the desirable culinary properties.
- It took years to realize that all trans fats did not have the same properties. Artificial trans fatty acids and ruminant *trans* fatty acids have entirely different properties in vivo as well as in vitro. Even small amounts of artificial trans fat affect the prostacyclin synthesis.
- When the amount of artificial trans fat in margarines was lowered the sudden cardiac death rate also showed a decrease.
- When *trans* fats are removed from the food supply, there will be 325,000 less sudden cardiac deaths per year.

Discovery of *trans* fats

Hydrogenation was discovered by Nobel laureate Paul Sabatier in the late 1890s. He worked with hydrogenating only vapors. In 1901, a German chemist named Wilhelm Normann showed that liquid oils could be hydrogenated, and patented the process in 1902¹. Production of the hardened fat commenced in 1909. Procter & Gamble acquired the US rights to the Normann patent and in 1911 they began marketing the first PHOs (partially hydrogenated oil). Hydrogenated fat began to replace lard in the 1920s. PHOs had desirable culinary properties as they had melting points close to body temperatures and became liquid in the mouth like butter. Prior to 1910, dietary fats consisted of butterfat, beef tallow, and lard. In 1910, no one knew what effect PHOs would have on the health of Americans. The effects *trans* fat in PHOs have on prostacyclin synthesis are now known². The present mix of dietary fat in the marketplace results in less prostacyclin synthesis, which is an important factor in cardiovascular health^{3a,4a}. Prostacyclin is a dominant prostaglandin produced by endothelial cells in arteries and is a potent vasodilator and inhibitor of platelet aggregation and leukocyte adhesion⁵. It limits the response to thromboxane, which is a potent inducer of vasoconstriction and platelet adhesion on the arterial wall and is partially responsible for the interruption of blood flow⁶. The rise of artificial *trans* fats in the diet correlates to the rate of American age-adjusted heart disease-related deaths since 1910^{7a}.

Composition of *trans* fats

It took nearly five decades before the biochemical structure of *trans* fatty acids were understood. In 1952, the gas chromatography was made available⁸ and could identify the components of PHOs. The partial hydrogenation of soybean oil added atoms of hydrogen to 50% of the bonds 9,12 in linoleic acid (n-6) and the bonds 9,12,15 in linolenic acid (n-3), converting them to 50% stearic acid⁹. Forty to fifty percent of the double bonds of fatty acids in n-6 and n-3 were shifted to different positions on the carbon chain making 9 different synthetic *trans* fatty acids and 5 different *cis* fatty acids. These were *cis* and *trans* isomers of octadecenoic and octadecadienoic acids that are not present in animal fats or plant oils. They

interfere with the action of two isoforms a constitutive COX-1 and an inducible COX-2 enzyme^{4b,10}. COX-2 is the enzyme that recognizes the isomers produced during hydrogenation as a foreign substrate and reacts to them by causing inflammation and inhibition of arachidonic acid, which is necessary to make prostacyclin. The 14 synthetic fatty acids were a source of energy but interfered with the conversion of n-6 to arachidonic acid and n-3 to eicosapentaenoic acid¹¹.

Several studies have called the attention to the *trans* fatty acids (TFAs) present in margarines and shortenings with some success. Samples of tissue obtained from human autopsies were shown to contain up to 14% TFAs¹². Samples of fat from human placental, maternal, fetal and baby tissue were also examined for the presence of TFAs¹³. While the maternal tissue contained considerable amounts of TFAs, these lipids were not found to any measurable extent in placental, fetal or baby fat¹⁴. This was also shown in rats that were fed *trans fat*. When the *trans fat* was removed from the diet, their tissue metabolized the *trans fat* and their tissue no longer contained *trans fat*¹⁵. The results of these studies indicated that the TFAs present in human tissue apparently arise solely from dietary fat, and they do not normally appear in the tissues unless a source of TFAs is included in the diet.

Differences between PHOs and ruminant fats

It was believed by the FDA that partially hydrogenated soybean oil *trans fat* had the same chemical structure and worked the same way in our bodies as natural vaccinic acid¹⁶. These two *trans fat* sources have entirely different properties *in vitro* as well as *in vivo*.^{3b} The elaidic acid in PHOs has a double bond at position 9, while the vaccinic acid in ruminant fats is at position 11. The enzymes in the body recognize vaccinic acid (butterfat and beef fat) as the fatty acid that has been in the diet for untold generations.

***In vitro* and *in vivo* study**

An *in vitro* study showed that the fatty acids in partially hydrogenated fat had different properties than fatty acids in animal fat or vegetable oil¹⁷.

Trans acids increased the incorporation of $^{45}\text{Ca}^{2+}$ into the cells, whereas *cis* acids did not incorporate $^{45}\text{Ca}^{2+}$ into the coronary artery cells. An *in vivo* study showed that the TFAs inhibited the synthesis of arachidonic acid, a polyunsaturated fatty acid, in the phospholipid membrane of arterial cells¹⁸. It was concluded that dietary *trans* fat perturbed essential fatty acid metabolism, which led to changes in the phospholipid fatty acid composition in the arterial wall, the target tissue of atherogenesis. Partially hydrogenated fat is a risk factor in the development of coronary heart disease because arachidonic acid is needed to synthesize prostacyclin.

Data from the CDC

Data obtained from the Center of Disease Control (CDC) shows the rate of death started increasing in 1910 and continued until 1968^{7b}, at which time the industry lowered the percentage of trans fat from 44% to 27% and increased the amount of linoleic acid from 8% to 25%^{3c}. In 1968 the age-adjusted rate of heart disease-related deaths began to decrease^{7c}. Data from the CDC states that almost 600,000 Americans died of heart disease in 2011, 325,000 of those from sudden cardiac death¹⁹. The other 275,000 deaths were due to calcification of the coronary arteries to 100% occlusion^{3d}.

Tentative determination to ban PHOs

On November 7, 2013 a tentative determination regarding PHOs was released by the FDA^{20a}. It stated that PHOs, which are a primary source of industrially-produced *trans* fatty acids or *trans* fat, are not generally recognized as safe (GRAS) for any use in food. The FDA requested comments of scientific data and information on this determination giving 60 days for responses. Before the 60 days were over they extended it another 60 days. That extension was over March 8, 2014. The FDA released this information in the Federal Register on November 8, 2013, “*trans* fats are an integral component of PHOs and are purposely produced in these oils to affect the properties of the oil and the characteristics of the food to which they are added.”^{20b} At zero percent of *trans* fat content in the body, the

prostacyclin release from vascular endothelial cells is 38.7 ng/mg of cell protein^{3e}. Data released in the Federal Register states that in 2012, the average American consumed 2.1 grams of trans fats per day, with the 90% percentile consuming 4.2 grams per day^{20c}. While consuming 2.1 grams of *trans* fat per day, the arterial cells will release 25 ng/mg cell protein, which is a significant drop from 38.7 ng/mg at zero percent. Consuming 4.2 grams/day of *trans* fat the cells will only release 15.5 ng/mg cell protein^{3f}. As more grams per day of *trans fat* are consumed, prostacyclin release from vascular endothelial cells to cell protein will decrease, proving an inverse relationship between the two processes. With the determination finalized the food manufacturers are no longer be permitted to sell PHOs without prior FDA approval.

Expert Opinion

The partial hydrogenation of vegetable oils have been shown to have an adverse effect on Americans. The FDA believed that artificial *trans* fats had the same chemical structure and worked the same way in the human body as natural trans fats. It has been shown that this is not true. The FDA finalized their decision to make artificial trans fat non-GRAS giving the industry three years to comply. With this decision more lives will be saved.

Funding for this type of research is difficult to find when one does not believe the mainstream about cholesterol and *trans* fats. The belief that heart disease is not a disease but a somatic response to a simple error involving the effect of *trans* fat in partially hydrogenated oil on prostacyclin synthesis goes against the mainstream. Therefore the present mix of dietary fat in the marketplace results in less prostacyclin synthesis and more sudden cardiac death.

In spite of the fact that the author has found an answer to heart disease and has convinced the FDA to consider making *trans* fats non-GRAS, he still has not received funding to continue his work.

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Chapter Five

Industrial Control of Guidelines for Lipid Nutrition

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Abstract

During the past half century, lipid nutrition has been strongly affected by the cholesterol hypothesis which states that increasing the intake of linoleic acid (ω -6) while reducing cholesterol and saturated fat is effective in lowering blood cholesterol and thereby reduces coronary heart disease. Even after the accumulation of enough evidence which indicate the fall of the hypothesis, pharmaceutical and food industries continue to advocate the risks of cholesterol and saturated fats, possibly to secure the profits of cholesterol lowering drugs and foods. Farming and livestock industries are closely associated with each other through seed oils. The established framework in the agricultural field involves seed oils containing linoleic acid and toxic components which might endanger human health when ingested chronically in large amounts. So far, industrial people, administration and associated scholars have been trying to hide the harmful aspects of vegetable fats and oils. In this review we emphasize that the safety of some vegetable fats and oils is an urgent problem to be addressed, and international collaborative research is necessary, to solve the problem rather than try to hide the facts from general public.

Introduction

After World War II, when the production of grains exceeded the levels that suffice human demands, excess grains began to be fed to livestock. Grains such as corn, soybean and rapeseed were chosen because of good productivity, amino acid score and other nutrient contents. However, since these grains contain too much oil for the health of herbivores, the oils were expressed. The remaining grains' meal was fed to livestock and the oils to humans. Such

agricultural changes occurred from around 1965 toward 1975 in Japan, and some Western industrialized countries preceded Japan by several years. These industrial and nutritional changes were supported and accelerated by Keys’ and Hegsted’s equations published in the 1950’s proclaimed that elevating polyunsaturated to saturated fatty acid ratio of ingested foods and reducing cholesterol intake are effective ways to lower plasma cholesterol levels and thereby reduce cardiovascular disease (CVD).

What we would like to emphasize here is that this agricultural and nutritional framework has been maintained firmly up to now, and any changes affecting this framework would cause conflict of interest among exporting countries (India, EU, USA, Canada) and importing countries (China, Japan, Mexico) of the seed oils. For example, evidence that excessive intake of linoleic acid causes many chronic diseases (Okuyama H et al., 1996) would be disadvantageous to the grain producers and food industry producing high linoleic acid foods, similarly to how critical evaluations of cholesterol lowering drugs are not welcomed by statin-related industries.

When scientists cannot reach agreement through publications, and the general people cannot judge scientists’ discussions, people tend to seek the recommendations from authoritative organizations such as World Health Organization (WHO) and Food and Agriculture Organization (FAO) in the United Nations. However, more than half of the budget of WHO comes from global industries and the presence of routes for specialists from industry to express their opinions as those of WHO are officially established? Therefore, serious questions arise as to whether the guidelines from these organizations are based on scientific evidence without being affected by their budget supporters. More specifically, The Codex Alimentarius from WHO/FAO is a set of international standards for food labeling and safety.

TABLE 1 Codex General Standard for the Labelling of Prepackaged Foods, specified for fats and oils, and Our Proposal for Classification of Fats and Oils.

Codex Classification

Except for those ingredients listed in section 4.2.1.4, and unless a general class name would be more informative, the following class names may be used.

| Name of Classes | Class Names | Additional Remarks |
|--------------------------------|-------------|---|
| Refined oils other than | Vegetable | Hydrogenated or partially hydrogenated as appropriate |

| | | |
|---------------------|---------------|--|
| olive | oil | |
| | Animal oil | — |
| Refined fats | Vegetable fat | — |
| | Animal fat | Pork fat, lard and beef fat shall always be declared by their specific names |

Our proposal for the classification of fats and oils

| Name of Classes | Class Names | Remarks |
|-------------------------|--|---|
| Vegetable fats and oils | Soybean oil, rapeseed oil, perilla oil, hydrogenated soybean oil etc.* | Type of fats and oils should be clarified |
| Animal fats and oils | Butter, lard, beef fat, fish oil, hydrogenated fish oil etc. | |

* A type of oil with a significant difference in fatty acid compositions may be classified as, e.g., high-oleic or high-linoleic safflower oil, and fractionated oil as high-oleic or high-palmitic palm oil.

According to the “CODEX GENERAL STANDARD FOR THE LABELLING OF PREPACKAGED FOODS (CODEX STAN 1-1985, refined oils other than olive oil are classified either as “vegetable oil” or “animal oil” (Table 1.), and refined fats as vegetable fat or animal fat. It is noted that the animal fat shall always be declared either as pork fat, lard and beef fat. In contrast, all types of vegetable oils could be labeled as vegetable oil.

This standardization of labeling of fats and oils does not appear to be scientific. Lard is a purified pork fat and there is no need to differentiate these two; the pork fat should be replaced with butter with fatty acid and minor component compositions significantly different from those of beef fat. Moreover, we have emphasized that various vegetable oils differ not only in their fatty acid compositions but also in minor components which exert significantly different physiological activities (Okuyama H, 2007a). Codex Alimentarius, just issued last year from WHO/FAO as labeling standard for packaged foods, does not appear to be evidence-based, but to be skewed by the influence of seed oil exporting countries and associated industry people who do not want to discuss the nutritional differences among different types of vegetable fats and oils (more detail in the sections II and II).

In Japan, committee members selected by the government tend to depend too much on the guidelines from WHO and world-leading medical societies of the US, simply translating them to people rather than evaluating and judging the available information by themselves. Currently, it is time for the general public to realize that nutritional and medical guidelines from the so-called authoritative organizations are likely to be seriously skewed by industry-supported scholars.

I. Fall of the cholesterol hypothesis, which has not been accepted by WHO and AHA

I-1. “The Cholesterol Myths” showing evidence against the “Cholesterol hypothesis”

A pioneering book by Uffe Ravnskov, “The Cholesterol Myths” was published in 2000. He collected many lines of evidence that contradict the cholesterol hypothesis defined above. In many countries, there have been scientists who disagree with the cholesterol hypothesis, but they encounter difficulties in publishing their opinions in established medical journals. Ravnskov directed a group of these people gathered under THINCS, The International Network of Cholesterol Skeptics. In the meantime, the mainstream scientists supported by the related industries continued to maintain their belief in the cholesterol hypothesis, ignoring opinions from THINCS, and the two groups’ arguments have not been on the same wavelength. Why have the scientific arguments on the cholesterol hypothesis continued for so long after the fall of the hypothesis became clear? The answer is probably simple; there are scientists who derive great benefits by laying smoke screens on the criticisms and prolonging the arguments or they lack the ability to critically evaluate the presented data.

Because of the onset of unethical problems associated with the reports on clinical trials performed mainly by industry-associated scientists, a penal regulation for performing clinical trials came into effect in the EU in 2004, which was quite effective in changing the evaluation of cholesterol-lowering medications; randomized controlled trials of statins revealed no significant beneficial effects for the prevention of coronary events despite significant decreases in LDL-cholesterol levels (de Lorgeril M, 2008). Even now, scientists continue to claim that benefits of statins (prevention of CVD) outweigh their adverse effects (onset of diabetes and other adverse effects)

based on meta-analyses of clinical papers published both before and after 2004. However, we did not adopt conclusions from meta-analysis of clinical papers including those published before 2004, mainly in 1990s', as reliable when we published a new cholesterol guideline 2010 (Okuyama H, 2011).

I-2. Fighting with the cholesterol guidelines issued from medical societies in Japan – high cholesterol level is a predictor of longevity

Japanese cholesterol guidelines for the prevention of CVD used to be issued from the Japan Atherosclerosis Society (JAS) supported by 9 related medical societies (JAS guideline). At the end of the last century, when the tentative guidelines were opened for discussion, the contents were essentially the same as those in ATP III (Adult Treatment Panel III) from the National Institute of Heart, Lung and Blood Institute, USA. In 2001, we challenged these guidelines by pointing out that the risk of high cholesterol level is variable depending on the populations examined; the relative risk of high cholesterol for CVD is as high as >5 when the population or subpopulation includes a high proportion of familial hypercholesterolemia (FH), but no positive associations or even inverse associations are seen between these parameters when the proportion of FH is lower; e.g., among general populations over 40~50 years of age (Okuyama H, 2007; Japanese edition in 2002). The Japan Atherosclerosis Society and related medical societies have been ignoring our proposal, and have continued to publish new guidelines based on “the lower, the better hypothesis” in 2007 and 2012, regardless of our new guidelines in 2010, and the latest guidelines by Hamazaki T et al., 2015.

During the past couple of decades, biological and pharmacological researches on statin actions have been rapidly in progress. Analyzing such results, we reached the conclusion that statins stimulate atherosclerosis and heart failure (Okuyama H, 2015). As the latest message from us forwarded to medical societies is gaining increasing number of supportive comments among internet information, we are optimistic in reaching an agreement among the world medical societies on the cholesterol guidelines for the prevention of CVD, diabetes and other lifestyle-related diseases, that is, high plasma cholesterol is a predictor of longevity and statin-applicable cases are extremely restricted, if any.

I-3. Dietary lipids with high $\omega 6/\omega 3$ ratios as a major risk of CVD and other

lifestyle related diseases

During the last century, large-scale dietary intervention trials based on the cholesterol hypothesis were performed and were unsuccessful. Helsinki Mental Hospital study (Miettinen M, 1972) is often cited as a successful trial, but it was a 6-year crossover study, which is too short a time to estimate the effects of dietary lipid intervention on CVD. In the Helsinki Businessmen study (Strandberg TE, 1991), increased mortality rates for CVD and all causes became clearer after 10 years of dietary intervention that was essentially based on the cholesterol hypothesis (Fig. 1). Thus, we should not cite the Helsinki Mental Hospital study as the one that showed the effectiveness of increasing polyunsaturated/saturated ratios and reducing cholesterol intake for the prevention of CVD; The Helsinki Businessmen study revealed that it is in fact the opposite.

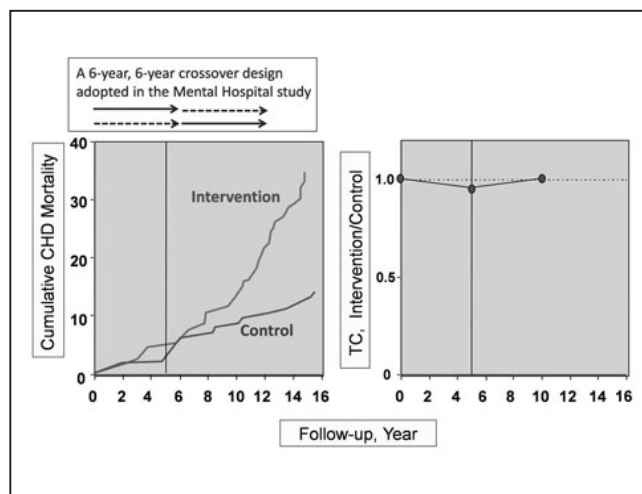


FIGURE 1 Helsinki Businessmen study

This is the first long-term (15 years) dietary intervention trial. For the beginning 5 years, hypocholesterolemic and hypotensive drugs were used, and dietary intervention was continued throughout the 15 years. Plasma cholesterol levels at 10 years of intervention were similar between the control and intervention groups (Strandberg, 1991). In the inserted square, the 6-year, 6-year crossover study schedule of the Helsinki Mental Health study (Miettinen M, 1972) is shown for comparison.

We would like to introduce an early example of papers that were distorted by industrial influence. The Helsinki Businessmen study was extended to 28 years (essentially it was 18 years, 3 years extension from the initial study of 15 years) (Strandberg TE, 1995), and new groups were added for the analysis beside the control and intervention groups; Low risk group, Excluded group, Refused group, and Dead in 1974 group. However, adding these new groups

with background data much different each other is not rational even though the authors claim that multivariate adjustment was performed. The conclusion starts with “The traditional risk factors (smoking, blood pressure, and cholesterol) are significantly associated with 28-year mortality”. However, the data do not support this statement. We interpret that only the Control and Intervention groups are to be compared in this trial. The death rates during the 18 years in the control group (n=610) and intervention group (n=612) were 31.1 and 63.7 (coronary heart disease); 1.6 and 26.1 (violent death, not natural death); 106.6 and 155.2 (all- cause deaths). We suspect that the above conclusion is a result of compromise among people in different fields.

The latest paper on large-scale dietary intervention based on the cholesterol hypothesis was published recently (Ramsden CE , 2013; Sydney Diet Heart study), which observed that substituting dietary linoleic acid in place of saturated fats increased the rate of death from all causes, coronary heart disease and cardiovascular disease. Based on the results, the Editorials of British Medical Journal softly criticized American Heart Association’s advisory that higher [than 10 % of energy] intakes [of ω -6 PUFAs] appear to be safe and may be even more beneficial may be misguided (Calder P, 2013).

Long term ingestion of lipids with high ω 6/ ω 3 ratios increase arachidonate/EPA ratio or arachidonate/(EPA+DHA) ratio of membrane phospholipids, and over production of ω -6 eicosanoids is the major cause of CVD, many types of cancer and other allergic, inflammatory diseases currently prevailing (Lands WEM, 2005; Okuyama H, 2007b, Ottoboni A, 2013). Nutritional, pharmacological, and gene technological means have been used to reach this conclusion.

Now it is clear why WHO and other organizations cling to the cholesterol hypothesis when scientific evidence warns of the prevalence of “excessive linoleic acid syndrome” (Okuyama H, 1996). Industrial power from countries exporting seed oils enriched with ω 6 fatty acids and the production of foods enriched with such seed oils incomparably outweighs the power of scientific evidence. Guidelines advising an increase in linoleic acid (ω -6) intake far above its essential amounts (1 energy %) are not evidence based, and are likely to be affected by industrial interests; the intake of 2 to 3 energy % is enough (International Society for Study of Fatty Acids and Lipids, ISSFAL).

II. Regulation of industrial *trans* fat based on inconsistent lines of evidence

II-1. Similarity of industrial and ruminant *trans* fats in physicochemical, biochemical and hypercholesterolemic properties

WHO and Food and Drug Administration (FDA, USA) have taken the initiative in excluding partially hydrogenated vegetable oils from our food and setting an upper limit of industrial *trans* fat at below 1 en%. Many Western countries appear to follow the WHO regulation, but the Japanese government decided not to set legal regulation of *trans* fat. This is because the average intake of *trans* fat was 0.7 en% a decade ago, now it is 0.3 en % and before long it is expected to be negligible. Situations are similar worldwide because alternative oil, palm oil, is available at much lower costs, and the shift from margarine to palm oil is clearly seen in the US (Fig. 2).

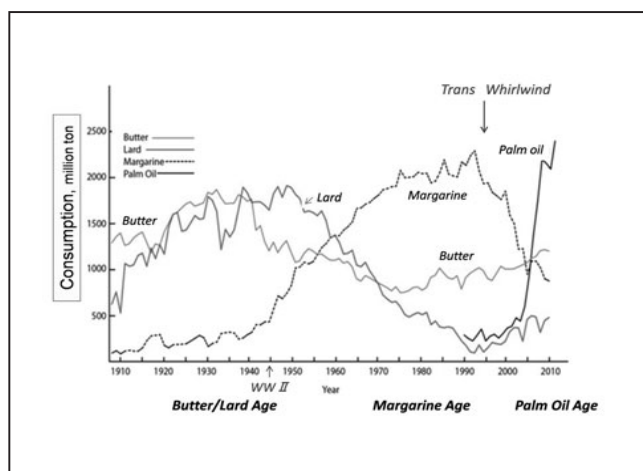


FIGURE 2 Trends of Fat Consumption in the US

WWII, the end of the World War II. Data taken from <http://www.cnpp.usda.gov/USFoodSupply-1909-2010>.

The necessity of regulating *trans* fat intake was based on reports that ingestion of *trans* fat elevates plasma LDL-C/HDL-C ratio and thereby increases CVD events. However, high LDL-C/HDL-C ratio is not a causative factor for CVD as explained in section I and elsewhere (Okuyama H, 2011; Hamazaki T, 2015).

In the regulations of Western countries industrial *trans* fat in partially hydrogenated oils is the target but not ruminant *trans* fat in foods of ruminant animal origin. This difference came from different physiological effects on CVD and diabetes in epidemiological studies as shown in Fig. 3.

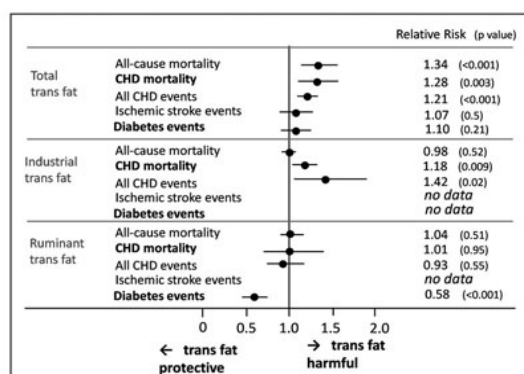


FIGURE 3 Effect of the types of *trans* fat intake on CVD and diabetes

Data from de Souza RJ, 2015.

Interestingly, industrial *trans* fat intake was positively associated with CHD mortality but not ruminant *trans* fat. Moreover, ruminant *trans* fat intake was inversely associated with diabetes but not total *trans* fat intake. Unfortunately, data for the correlation of industrial *trans* fat intake and diabetes are not shown. This set of data in Fig. 3 is enough to convince people that industrial *trans* fat and ruminant *trans* fat must be regulated separately, but this raises a serious question. What is the difference between the two types of *trans* fats?

Trans octadecenoic acids (18:1) consisted of 17 positional isomers with a *trans* double bond located at 2 to 17 position numbered from the carboxyl terminus, and the major isomers of the two types of *trans* fats and respective melting points are shown in Fig. 4.

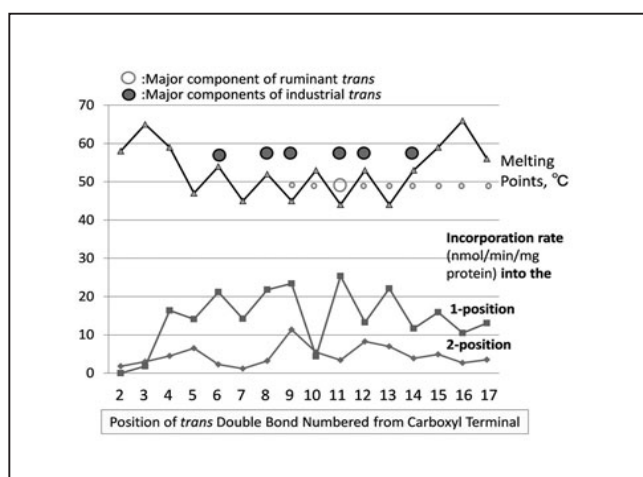


FIGURE 4 *Trans* octadecenoic acid isomers (18:1) and their properties

Respective melting points and incorporation rates into the 1 and 2-positions of phospholipid by acyl-CoA:lysophosphatidylcholine acyltransferase system in rat liver microsomes are presented (Okuyama H, 1972).

Although each isomer has slightly different physicochemical and biological properties (Fig. 4), those of major industrial *trans* isomers and ruminant *trans* isomers as a whole are relatively similar, and no crucial difference to account for the observed difference in the effects on CVD and diabetes (Fig. 3) could be found from Fig. 4. Consistently, both industrial and ruminant *trans* fat exhibited similar effects on plasma lipid levels in human studies; ruminant *trans* fat exhibited even greater activity to elevate LDL-C level and TC/HDL-C ratio (Fig. 5).

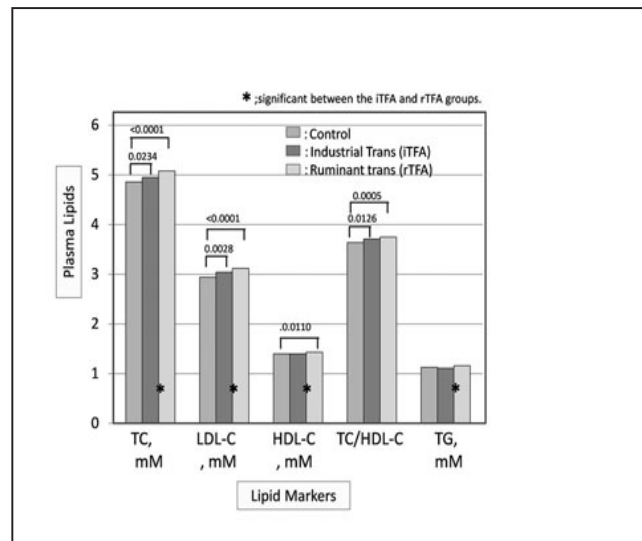


FIGURE 5 Randomized, controlled study comparing the effects of industrial and ruminant *trans* fats on plasma lipid levels in healthy volunteers

Healthy participants ($n=106$, 47 ± 10.8 years of age, $BMI=28.5\pm4.0$) were randomly assigned for a 24 days cross-over trial. Control diet (33 en% lipid) was supplemented with 3 en% industrial *trans* fat (iTFA), 3 en% ruminant *trans* fat (rTFA, vaccenic acid), or 1 en% $c9,t12$ -CLA (conjugated linoleic acid). Data taken from Gebauer SK, 2015.

US Department of Agriculture (USDA) has the facility and experience to perform dietary intervention trial controlling whole nutrients, and concluded that ruminant *trans* fat should also be included in the regulation of *trans* fat. In fact, the data shown in Fig. 5 are apparently inconsistent with the results shown in Fig. 3, which raises a possibility that factor(s) other than *trans* fat per se may be involved in the differential correlation of the two types of *trans* fats with CVD and diabetes (Fig. 3), which will be explained in section II-3.

II-2. Safety of the alternative oil, palm oil, is of serious concern

Palm oil was chosen in the US, Japan and UK as the alternative to hydrogenated vegetable oils. Earlier, palm oil was not used as food but purification methods were improved, and now is the second most consumed vegetable oil in Japan. However in animal experiments, palm oil exhibited unusual survival shortening activity in mice (Fig. 6). Although this research report was published from National Food Research Institute Japan, and the experiment was stopped half way in, the results raise a serious concern on the safety of palm oil that should not be overlooked.

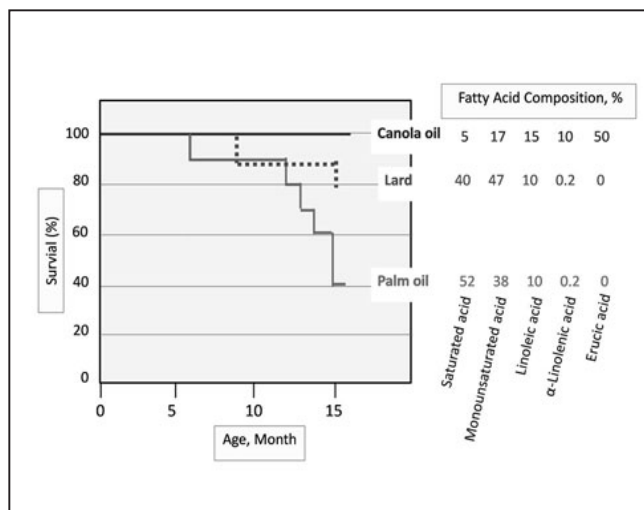


FIGURE 6 Effects of dietary vegetable oils on survival of mice

Diet containing 6 w/w % of oil was fed to male ICR mice (n=10 in each group). Data taken from Suzuki H, 1991.

Colon carcinogenesis is known to be promoted by linoleic acid (ω -6) and suppressed by α -linolenic acid (ω -3). The arachidonic acid (ω -6) cascade is involved in colon carcinogenesis, and anti-inflammatory drugs and genetic manipulation to suppress this cascade are effective in suppressing the carcinogenesis in animal experiments. Palm oil is not rich in linoleic acid but colon carcinogenesis was greatly promoted by dietary palm oil (Fig. 7) (Narisawa T, 1991). Similarly, unusual hyperinsulinemia of palm oil observed in diabetic mice (Ikemoto S, 1996) and stroke-stimulating activity observed in SHRSP rats were not accounted for by its fatty acid composition.

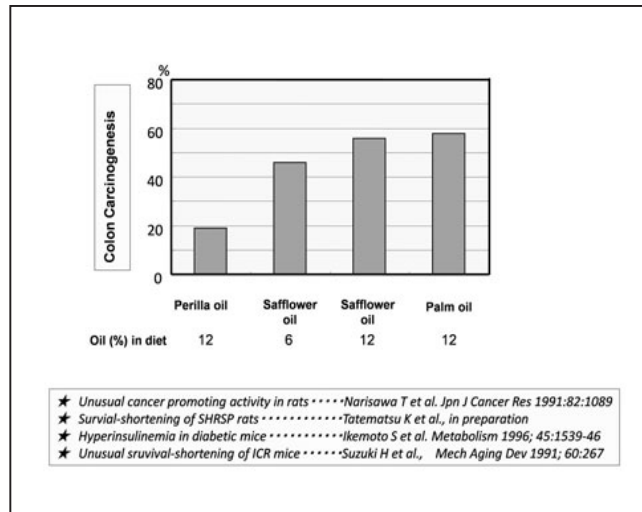


FIGURE 7 Palm oil used as an alternative to hydrogenated oils is not safe – colon cancer-promoting activity and some adverse effects

See text for explanations. Data taken from Narisawa T, 1991.

These results from animal experiments raise serious questions on the safety of palm oil, and does not support the industry guided shift from butter and lard to palm oil. As noted above, this shift is going to be completed before long in Japan. The oil and seed oils meal industries as well as associated administrative people in Japan have made no efforts to inform people of the potential health hazards.

II-3. Vitamin K₂ inhibitors rather than industrial trans fat as a causative factor of CVD and DM

Soybean oil and canola oil are rich in vitamin K1. When ingested, its side chain with one double bond is cleaved off to form vitamin K3, and then geranylgeranyl group with 4 double bonds (a prenyl intermediate in cholesterol biosynthesis) is inserted to form vitamin K2. (Fig. 8). In various tissues including brain, vitamin K2 level is higher than K1 and serves as a cofactor for enzymes to γ -carboxylate, the glutamyl residue of proteins. Statins inhibit the supply of geranylgeranyl residue and warfarin inhibits the reactivation of oxidized vitamin K1.

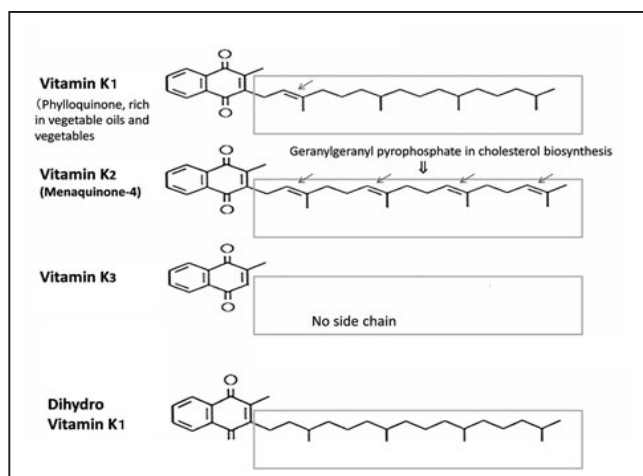


FIGURE 8 Metabolism of vitamin K1 to form vitamin K2 in mammals

See text for explanations.

Industrial hydrogenation of canola and soybean oils produces not only *trans* fat but also the dihydro form of vitamin K1 (dihydro-VK1), the side chain of vitamin K1 with one double bond being hydrogenated (Fig. 8). The dihydro-VK1 is not converted to vitamin K2, and inhibits the vitamin K2 dependent processes in human, e.g., bone homeostasis (Booth SL, 2001; Shea MK, 2009).

Recently, research on vitamin K2-dependent reactions is rapidly in progress, revealing the role of several proteins such as protein C, S, Z, matrix Gla protein, and osteocalcin (Ocn) in addition to well-known coagulation proteins. Intercellular Gla protein is γ -carboxylated and acquires the ability to bind calcium and thereby inhibit artery and kidney calcification. Undercarboxylated osteocalcin (uc-Ocn) is synthesized in osteoblasts in the bone, γ -carboxylated form c-Ocn, is accumulated in the matrix phase of bone. When osteoclasts work, acidic conditions are produced to convert c-Ocn to uc-Ocn (Shea MK, 2009; Oury F, 2013). Both c-Ocn and un-Ocn are excreted from the bone serving as bone-derived hormones in various organs as shown in Fig. 9. It is important to realize that inhibition of vitamin K2-dependent processes affects functions of most organs of the body through the bone-derived hormone, osteocalcin.

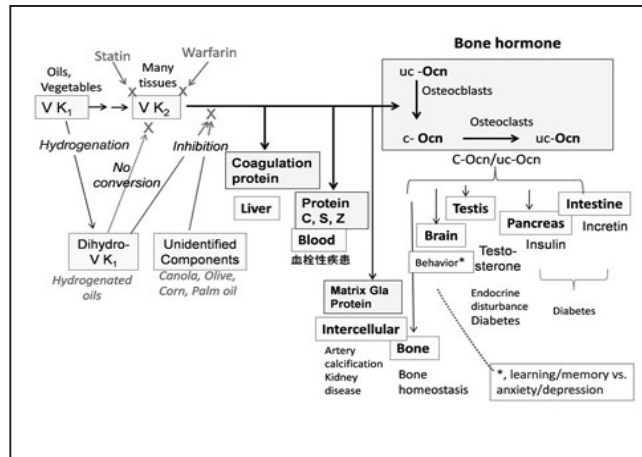


FIGURE 9 Inhibition of Vitamin K2-dependent processes induces diverse disorders

Partially hydrogenated soybean oil as well as canola and some other oils exhibits vitamin K₂-deficiency symptom such as hemorrhagic property, decreased platelet counts and kidney lesions (Okuyama H, 2007a; Hashimoto Y, 2014). Both c-Ocn and uc-Ocn from the bone are supposed to work on various target organs (Oury F, 2013).

We have been studying the effects of long-term feeding of vegetable oils in the stroke prone SHR (SHRSP) rat. As compared with soybean oil, canola oil and partially hydrogenated soybean oil and some other relatively common oils shortened the survival of SHRSP rats by accelerating cerebral bleeding, decreasing platelet counts, damaging kidney, and decreasing tissue testosterone levels, some of which are known to occur under vitamin K₂-deficiency. Together with the findings by Booth SL, 2001, Shea MK, 2009 and Ito A., 2011, dihydro vitamin K₁ was proposed as the active principle in hydrogenated soybean oil to shorten the survival of SHRSP rats (Okuyama H, 2007a).

Canola oil contains no dihydro-VK₁, but unidentified active principle in the oil exhibited similar inhibiting activity toward the vitamin K₂-dependent protein, osteocalcin; both exhibited decreased suppressive activity in the bone morphogenetic protein (BMP)-induced ectopic bone formation in mice (Hashimoto Y, 2013).

Coming back to the WHO regulation of industrial *trans* fat, we pointed out the following problems:

1. Elevation of LDL-C/HDL-C cannot be a causative factor of CVD because statins and statins plus CETP inhibitor therapies lower this ratio but exert no significant beneficial effect on CVD,

2. Industrial and ruminant *trans* fats elevate TC/HDL-C ratios similarly (Fig. 5), but only the industrial *trans* fat was positively associated with CHD mortality (Fig. 3),
3. Beneficial effect of ruminant *trans* fat, but possibly not industrial *trans* fat, for diabetes has not been explained (Fig. 3).

Instead, we interpret that industrial *trans* fat is the surrogate marker, and coexisting dihydro-vitamin K₁ is the active principle to inhibit the vitamin K₂-dependent activation of matrix Gla protein and osteocalcin, thereby accelerating artery and kidney calcification. Similarly, ruminant *trans* fat is the surrogate marker of vitamin K₂ because both ruminant *trans* fat and vitamin K₂ are rich in beef, milk and cheese. In fact, vitamin K₂ intake but not vitamin K₁ intake was inversely associated with mortality rates for all causes and CHD in Rotterdam study (Geleijnse JM, 2004), and similar association has been noted with metabolic syndrome markers (Shea MK, 2009).

The two different interpretations for the adverse effects of *trans* fat (Fig. 10) bring about definitive impact on human health. If the industrial *trans* fat per se is the active principle and the effect is only on CVD as explained in the WHO guidelines, the alternative oil, zero-*trans* palm oil, is ready to substitute for hydrogenated oils. In fact, industry people are trying to accelerate the shift from hydrogenated oil to palm oil as the latter is available at much lower costs, and sooner or later *trans* fat problems will disappear from media world (Fig. 10).

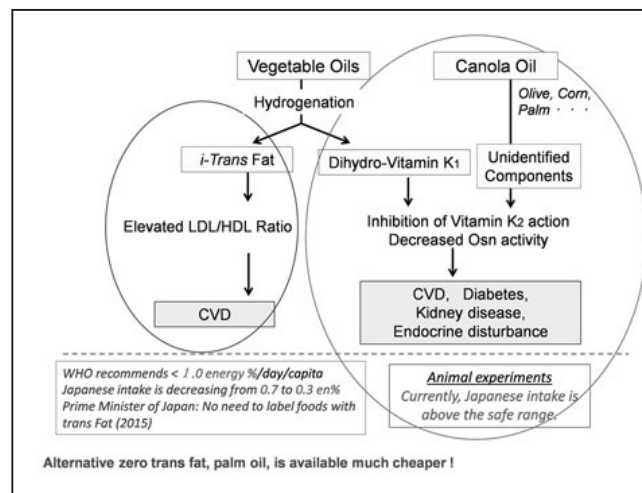


FIGURE 10 Two different interpretations for the adverse effects of hydrogenated oils on CVD

See text for explanations.

Contrarily, if our interpretation (Fig. 10) is applicable to food industry, the adverse effects of canola oil and some other vegetable oils need to be solved or human intake of these oils should be reduced (more details in section III).

III. Improved rapeseed quality and its toxicity

III-1. A historical overview of the improvement of rapeseed quality

According to a review by Schmid A and Schmid H, 1992, rapeseed has been planted in central Europe mainly for lighting but rarely for eating. However, rapeseed cake was recognized in 1980s' to cause toxicity in hen and ruminant animals, the problem of which was apparently solved by setting upper limits of rapeseed meal to be fed to livestock (Fig. 11).

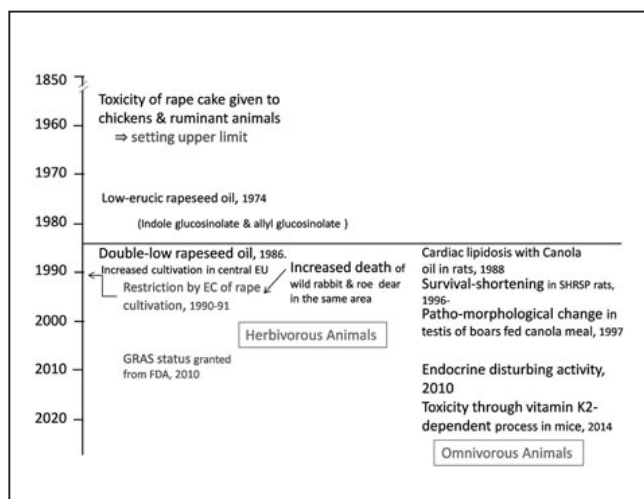


FIGURE 11 Toxicity of rapeseed (Canola) in mammals and the administrative steps taken

See text for explanations.

Erucic acid with 22 carbon chain and one double bond is an active constituent of rapeseed to cause lipidosis in the heart. Other toxic components are indole-glucosinolate, allyl-glucosinolate (Fig. 12) and their metabolites such as isothiocyanates, thiocyanates, nitriles, anti-thyroid agent (goitrin), S-methylcystein sulfoxide and dimethyl disulfide. These components affect many tissues but noteworthy are the rapeseed blindness and behavioral disorder (psychosis) observed in herbivores.

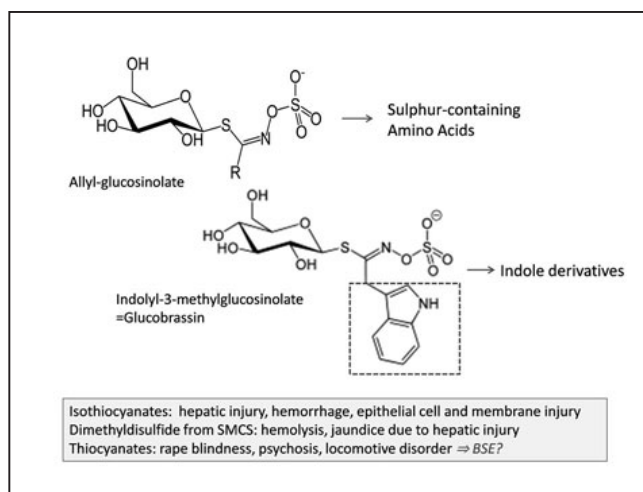


FIGURE 12 Glucosinolates as toxic materials of rapeseed oil

See text for explanations.

In 1974, low-erucic rapeseed variety was selected and then a double-low rapeseed with much lower levels of glucosinolate was established in 1986, and canola was used as a brand name for a double-low cultivar. Then, the cultivation of double-low rapeseed increased in central Europe. Along with this increase, the numbers of wild rabbit and roe deer decreased significantly in this area, and the European Commission restricted the rapeseed cultivation in 1990-91. Even the double-low rapeseed does not appear to be safe in herbivores (Schmid A, 1992). It is difficult to understand why anyone would think it safe to consume seeds capable of killing wild rabbits and deer. Wild animals are by their nature much more healthy and robust than domestic or laboratory animals.

A Putative Story on Mad Cow Disease and Rapeseed

The rapeseed toxic components caused the so-called rapeseed blindness and behavioral disorder (psychosis) in herbivores, which is similar to BSE (bovine spongiform encephalopathy or mad cow disease) and CWD (chronic wasting disease) of wild deer shaped (fed) with grains to raise large antlers in northern America. The area where wild deer migrate is said to overlap with the area where wild rapeseed grows. These are the part of the observations for the proposal that rapeseed rather than an infectious prion may be the cause of mad cow disease and chronic wasting disease, and we support that this proposal is still considered valid. This theory lacks objective evidence but there may be additional hidden evidence. As a matter of fact, no positive

correlation has been found between meat and bone meal (MBM) and BSE in Japan.

Despite these observations, we find no advice from the EC regarding the safety of double-low rapeseed oil, and US Food and Drug Administration later granted GRAS (generally regarded as safe) status to rapeseed oil for human use (2010). It is said that the Canadian government spent US\$50 million to get it approved (Foodprints • Health & Nutrition. The Inconvenient Truth About Canola Oil. Original article at: <http://www.smallfootprintfamily.com/the-inconvenient-truth-about-canola-oil#ixzz3xVciuab9>).

III-2. Toxicity of double-low rapeseed oil and some other vegetable oils

In omnivorous animals, canola oil was reported to cause lipidosis in the rat heart (Magnuson BA, 1988). However, various reasons were presented to minimize the impact of this finding. For example, the proportion of saturated fatty acids is relatively small in canola oil and no statistically significant lipidosis was observed when animal fats were given together with canola oil. Humans in general ingest relatively large amounts of animal fats so that the impact of canola oil induced lipidosis would be negligible in humans. Of course, dilution of canola oil with animal fats would result in reduced degree of lipidosis, but this does not ascertain the safety of long-term canola oil ingestion in humans. Apparently this problem seemed to be solved or covered up.

About a decade later, our group (Huang MZ, 1996) encountered an unexpected result; dietary canola oil and evening primrose oil greatly shortened the survival of stroke-prone, spontaneously hypertensive (SHRSP) rats compared with soybean oil, perilla(seed) oil and fish oil (Fig. 13). Fatty acid composition of oils does not account for the difference, and we postulated the presence of unidentified component(s) rather than fatty acids and phytosterols, because the free fatty acid fractions obtained after alkaline or lipase hydrolysis of canola oil exhibited no significant activity. Hydrogenation of canola was expected to lessen the toxicity but it augmented it.

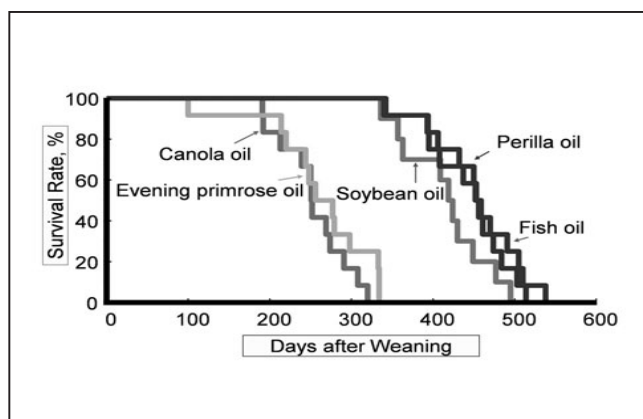


FIGURE 13 Effects of dietary oils on survival of stroke prone SHR rats

SHRSP rats (n=12/group) were fed a diet containing 10% (w/w) oil from weaning under ad lib conditions. Data taken from Huang MZ, 1996.

Dr. Lands WEM, former Professor, University of Michigan, advised one of us (HO) to see Dr. Bear-Rogers J, Health Canada and report the results to FDA (USA) and Ministry of Health and Welfare, Japan, so this was done around 1995.

Dr. Bear-Rogers is a very sincere, respectable scientist. Her group started experiments to confirm our experiments, informed us that olive oil and corn oil also exhibited survival shortening activity in SHR rats, and then she quit her position at Health Canada. One of the successors of the team, Dr. Ratnayake WM (2000) proposed that phytosterols may be the active principle (Ratnayake WM, 2000b), but olive oil was exceptional; it contains little phytosterol but shortened the survival comparably.

A research group supported by the Ministry of Health and Welfare Japan repeated the experiments but no action has been taken so far regarding the use of canola oil. Another ministry of Japan recommended and supported the cultivation of rapeseed, and every spring the fields filled with yellow flowers show up in newspapers emphasizing the ecological approach that the meal is used for livestock, oil for school children and flowers for sightseeing. We have emphasized that rapeseed oil should not be consumed, especially by children.

So far, canola, palm, olive, corn, high-oleic safflower, high-oleic sunflower, evening primrose oil, and partially hydrogenated soybean and traditional rapeseed oil have been shown to shorten the survival of SHRSP rats, and they are likely to contain unidentified inhibitor of vitamin K2-dependent processes. Animal fats such as butter and lard are safer in this animal model (Fig. 14).

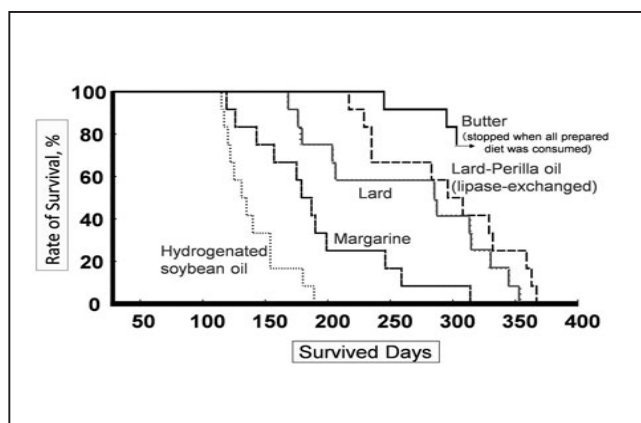


FIGURE 14 Comparison of survival-shortening activity of fats and oils in SHRSP rats

A diet supplemented with 10 (w/w) % of fat was fed to SHRSP rats (n=12 in each group). Data taken from Tatematsu K, 2004.

These chronic adverse effects observed in animal experiments are not easy to be examined in clinical trials. Therefore, the dose-response relationship in animal experiments is important to extrapolate the results to human nutrition. The survival-shortening activity of canola oil is dose-dependent, and a diet containing 6 energy % of oil still exhibited statistically significant activity. Currently, lipid energy % of ingested foods are around 25-35 % in most industrial countries, roughly half is vegetable oils in which more than 40 % is canola oil in Japan. Not only canola oil but also several other vegetable oils and hydrogenated oils exhibit comparable survival-shortening activities. Therefore, current Japanese intake of such oils is likely to be above the safe range without multiplying with the safety coefficient usually applied in toxicology field for the presence of species difference and difference among individuals (0.1 x 0.1). In Western countries where butter is still one of the major lipids consumed, the impact of these vegetable oils may be weaker. However, the EU seems to be one of great exporters and consumers of rapeseed.

The publications reporting these toxic effects of vegetable oils in rodents are listed in Table 2. Most of these reports are PubMed cited. Very importantly, however, the results of these publications, as well as adverse effects of high-linoleic vegetable oils, have been disregarded by WHO and major medical societies worldwide that are possibly supported by globally associated industries. Thus, the information unfavorable to the industry tends to be screened from the general public.

TABLE 2 Adverse activities of dietary rapeseed (canola) oil and hydrogenated soybean oil compared with perilla (seed) oil, soybean oil, linseed oil, butter and lard in rodents

| Publication | Animal | Major Results | Control oil |
|--|-----------|--|-------------------------------------|
| Huang MZ, Biol Pharm Bull 1996; 19:554-7 | SHRSP rat | Survival-shortening was dose- dependent, associated with cerebral bleeding, anal smudge and weight loss | Perilla oil, microbial oil |
| Huang MZ, Lipids 1997; 32:745-51. | SHRSP rat | Canola, high-oleic safflower, high-oleic sunflower, olive and evening primrose oil shortened the survival | Perilla oil, soybean oil |
| Miyazaki M, Lipids 1998; 33:655-61 | SHRSP rat | Hydrogenated soybean oil shortened the survival; toxic material was formed during hydrogenation | Soybean oil |
| Miyazaki M, Nutr Res 1998; 18: 1049-56 | SHRSP rat | Hydrogenation of canola and soybean oil did not reduce the toxic effect | Soybean oil |
| Miyazaki M, Biochim Biophys Acta 2000; 101-10 | SHRSP rat | Canola and safflower oil accelerated kidney injury | Soybean oil |
| Naito Y, Toxicol Lett 2000;116:209-15 | SHRSP rat | Canola oil induced shortening of blood coagulation time and increased fragility in erythrocyte membranes | Soybean oil |
| Ratnayake WM, Lipids 2000; 35: 409-20 | SHRSP rat | Canola and low-sulfur canola, olive oil and corn oil shortened the survival. Phytosterol content was inversely associated with survival. | Soybean oil and other types of oils |
| Ratnayake WM, J Nutr 2000; 130:1166-78. | SHRSP rat | High concentration of phytosterols make the cell membrane more rigid, which might be a factor contributing to the shortened life span. | Soybean oil, olive oil |
| Ogawa H, Clin Exp Pharmacol Physiol 2003; 30:919-24. | SHRSP rat | Five times more phytosterol was necessary to reproduce the activity of canola | Soybean oil |
| Naito Y, Toxicology. 2003; 187:205-16. | SHRSP rat | Promotion by canola oil of hypertension-related deterioration in organs was proposed to be related to shortened life span | Soybean oil |

| | | | |
|---|------------------|--|-------------|
| Tatematsu K, J Nutr 2004; 134: 1347-52 | SHRSP rat | Survival of offspring was affected by the diet that mothers took (2 generational study) | Soybean oil |
| Tatematsu K, Food Chem Toxicol 2004; 42:1443-51 | SHRSP rat | Factor(s) other than phytosterol, and tocopherol status is critical for the toxicity | Soybean oil |
| Tatematsu K, J Health Sci. 2004; 50:108-11 | SHRSP rat | Butter, lard and ester-exchanged lard- perilla were safer than canola | Butter |
| Ohara N, Food Chem Toxicol 2006; 44:952-63 | SHRSP rat | Toxicity and phytosterol were partially separated by CO2 supercritical extraction method | Soybean oil |
| Okuyama H, Lipids 2007; 42:821-5 (review) | SHRSP rat | Dihydro-vitamin K1 was proposed to be one of active principles in hydrogenated oils | Soybean oil |
| Ohara N, Food Chem Toxicol. 2008; 46:2573-9. | SHRSP rat | Supercritical CO2 extraction produced a safe fraction, though it failed to separate clearly the causative substances. | Soybean oil |
| Ohara N, Food Chem Toxicol. 2009; 47:157-62 | Wistar/Kyoto rat | Canola oil elevated BP, increased plasma lipids, activated G-6-P DHase, decreased platelet, shortened coagulation time and induced anomaly in the kidney | Soybean oil |
| Okuyama H, J Toxicol Sci 2010; 35:743-7 | SHRSP rat | Testosterone-lowering activities of canola and hydrogenated oil were detected | Soybean oil |
| da Coata CA, Horm Metab Res 2013; 45(9):652-4 | Rat | Canola impaired pancreatic functions | Soybean oil |
| Hashimoto Y, Toxicol Reports 2014; 1:955-62. | Mouse | Canola and hydrogenated soybean oil accelerated ectopic bone formation | Soybean oil |
| Cai J, Nutr Neurosci. 2014 May 26 | SHRSP rat | Canola accelerated cerebral breeding and decreased platelet counts | Perilla oil |

III-3. Principles of rapeseed toxicity and their physiological activities

Two kinds of glucosinolate, allyl- and indolyl-glucosinolate, and their metabolites have been identified as the major components exerting adverse and beneficial effects (Fig. 12). One of metabolites, S-methylcystein sulfoxide (SMCS) is an anemic factor observed in lamb and cow, and thiocyanates cause rape blindness and psychosis (behavioral disorder) (Schmid A, 1992). Indole carbinol, a metabolite of indolyl glucosinolate, is polymerized under acidic conditions of stomach, and a dimer, di-indolylmethane, is a ligand of Ah receptor which binds with allyl hydrocarbon such as dioxin (Bjeldanes, 1991).

Most glucosinolate metabolites identified so far are hydrophilic, and are expected to be washed out during the production of cooking oils. However, di-indolylmethane is likely to be in oil. The survival-shortening factor (s) is hydrophobic and alkaline- or lipase-sensitive, which may suggest the presence of hydrophobic moiety in the molecule. Recently, oil expression is being replaced by hexane extraction in industrial vegetable oil production. Then, the hydrophobic toxic factor would move to oil and the meal for livestock would be safer than before.

Even though the survival-shortening factor(s) in canola and some other oils have not been identified yet, its physiological activities have been clarified to the extent that cannot be disregarded. The mechanisms of action are similar, at least in part, to dihydro-vitamin K1 in hydrogenated soybean oil in that they interfere with vitamin K2 functions, one of the target organs of which is the testis (Fig. 9).

III-4. Endocrine disturbing activity of some vegetable oils

Based on the results from DNA microarray analysis, tissue steroid hormone levels were determined. In the serum and testis, testosterone contents of the canola oil group were significantly lower than in the soybean oil group but not corticosterone and dihydrotestosterone contents (Fig. 15) (Okuyama H, 2010).

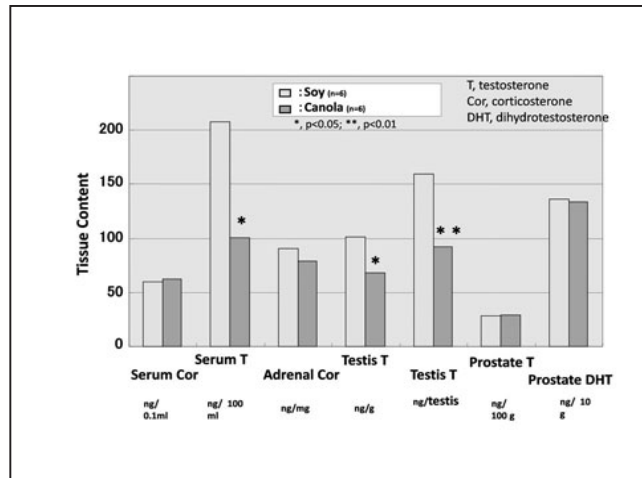


FIGURE 15 Tissue steroid hormone contents in SHRSP rats fed a diet supplemented with canola or soybean oil

SHRSP rats were fed a conventional diet supplemented with canola or soybean oil (Soy, 10 w/w%; 22 en %) from weaning (n=12 in each group). Data taken from Okuyama H, 2010.

In view of the importance of the observed endocrine disturbing activity of canola oil, experiments were repeated adding partially hydrogenated soybean oil group (Fig. 16). Both canola and hydrogenated soybean oil with a comparable survival-shortening activity lowered serum and testis testosterone contents, which was associated with altered survival of the second generation (Tatematsu K, 2004b).

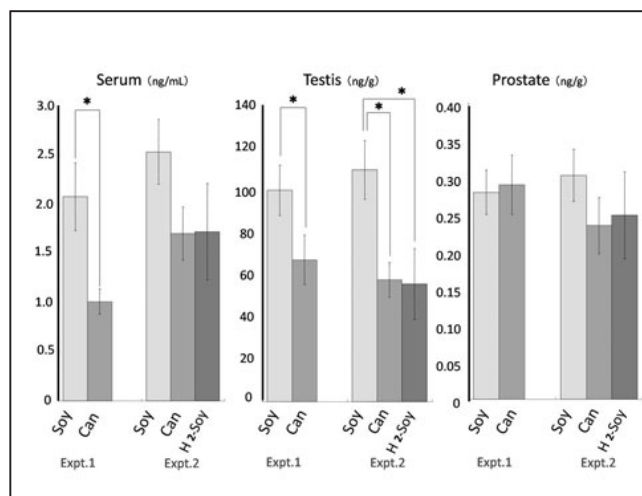


FIGURE 16 Effects of dietary oils on tissue testosterone contents in SHRSP rats

*Conditions for Expt. 1 were the same as in Fig.15 In Expt. 2, three groups with additional partially hydrogenated soybean oil (H2-Soy) group were compared. (Data taken from Okuyama H, 2010). *, $p < 0.05$*

Dioxins have been recognized as the most powerful endocrine disturbing substances. The dose of dioxins to lower testosterone level in animal experiments is >200 fold higher than the amounts average Japanese currently ingest (0.69 pg/kg body weight/day in 2012). However, the difference between these two doses is much smaller in the case of vegetable oils, and in fact, both are comparable (~6 en%). The mechanisms of vegetable oils to lower testis testosterone, and affect behavioral pattern through inhibition of vitamin K₂-dependent biochemical pathways have been gradually revealed. Osteocalcin synthesized in osteoblasts is γ -carboxylated to form c-Ocn, which is stored in the matrix phase of the bone. When osteoclasts are activated, acidic conditions are produced to decarboxylate c-Ocn to form uc-Ocn. Currently, it is believed that both c-Ocn and uc-Ocn are secreted from the bone, taken up by Leydig cells in the testis, modify gene transcription and stimulate testosterone production, and the testosterone stimulates spermatogenesis in the spermatocytes (Oury F, 2011).

It is interpreted that dihydro-vitamin K₁ in the hydrogenated oils and unidentified components in canola and some other oils with properties similar to dihydro-vitamin K₁ induce tissue vitamin K₂-deficiency, resulting in disorder of testis functions. Testis hypertrophy observed in canola meal fed boars, as compared with soybean meal (Rotkiewicz T, 1997), may be relevant to altered steroid hormone levels, just as both deficiency and overdosing of iodine induce thyroid hypertrophy. Admitting to make a leap from animal studies to humans, it may be noteworthy that vitaminK₂-deficient populations (Geleijnse JM, 2004; Geleijnse JM, 2011) as well as testosterone deficient populations (Khaw KT, 2007) exist in the contemporary societies generally eating enough foods, and that young men's sperm properties are poorer than those of a few decades ago (Iwamoto T, 2005; Anderson A-M, 2008).

Another endocrine disturbing substance is gossypol that is present in both the meal and oil from cotton seeds, which may have been clinically used in the case of one-child policy in an Asian country. A couple of decades ago, using cottonseeds for livestock was stopped in the Western countries, which is possibly associated with disorders of sexual cycle of cattle. Sooner or later, the production of cottonseed oil increased in Japan. Altogether, we propose that excessive intake of some kinds of vegetable fats and oils should not be disregarded when analyzing environmental factors causing endocrine disturbance.

IV. Industrial impacts on lipid nutritional guidelines for the prevention of lifestyle-related diseases

Lipid nutrition is involved in chronic diseases such as atherosclerotic CVD, diabetes, cancer, and other allergic, inflammatory diseases. Various fats and oils of animal and vegetable origin are characterized by their fatty acid compositions and minor component compositions. Animal experiments have been performed extensively since the latter half of the last century, and observational clinical studies followed. However, large-scale randomized, controlled studies on fats and oils in humans are limited. This is mainly because profits do not accompany the demonstration of new functions of known foods. Therefore, at present, lipid nutrition must be based mainly on basic research and observational human studies.

Fatty acid compositions of cellular lipids are known to differ among organs, but those of an organ are relatively similar among different species. For example, DHA is particularly rich in retinal lipids in mammals as well as in frogs and fish. This **high organ-specificity and relatively low species specificity** is one of the reasons to rely on animal experiments, although there may be cases when species' differences must be taken into consideration. In this chapter, we summarize briefly the results of nutritional evaluation of fats and oils, independently of the evaluation by authoritative organizations.

IV-1. Excessive linoleic acid (ω -6) syndrome

First, long-term ingestion of ω -6 fatty acids in the absence of competing amounts of ω -3 fatty acids leads to membrane phospholipids with elevated arachidonate (ω -6)/EPA (ω -3) ratio or arachidonate (ω 6)/(EPA+DHA) (ω 3) ratio, resulting in elevated inflammation. Persistent inflammation caused by stimulation of arachidonate cascade is a possible major cause of atherosclerotic diseases, cancer of adenocarcinoma type, and other allergic, inflammatory disease, which has been proven by nutritional, pharmacological and gene technological means as described in section I and elsewhere (Okuyama H, 1996, 2007; Kang JX, 2008).

Obviously, the above notion is disadvantageous to seed oil exporting countries and industries producing high-linoleic foods. In order to maintain the agricultural framework of farming and livestock industry, consuming all the oils produced annually is desirable. Accordingly, the guidelines for the

prevention of coronary heart disease issued from WHO and AHA (American Heart Association) still do not accept the positive associations with excessive intakes of vegetable oils with high $\omega 6/\omega 3$ ratios and lifestyle-related diseases. It is very difficult for us to believe that these guidelines were prepared simply based on scientific evidence.

- **WHO:** Prevention of cardiovascular diseases: guidelines for assessment and management of total cardiovascular risk, WHO Press, 2007
- **2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular Risk:** Eckel RH, Jakicic JM, Ard JD et al. *Circulation*. 2014; 129(25 Suppl 2):S76-99.

IV-2. Intentional regulation of trans fat

People welcomed the regulation of industrial *trans* fat led by WHO and FDA. However, some epidemiological studies were inconsistent with the causative role of dietary *trans* fat for atherosclerosis. Moreover, clinical study demonstrating comparable cholesterol-elevating activities of both industrial and ruminant *trans* fats (Fig. 5) is inconsistent with the regulation targeting industrial *trans* fat only as described above.

Another aspect is that statins are effective in lowering LDL-C/HDL-C ratio, and statin plus cholesterol ester transport protein (CETP) inhibitor combination is more effective, but they are ineffective in reducing CHD significantly, and a clinical trial with the latter increased all-cause mortality. Therefore, we wonder how the so-called authoritative organizations such as WHO and FDA can keep claiming that reducing industrial *trans* fat is effective for the prevention of CHD. The majority of citizens is not informed of this scientific evidence and simply follows the guidelines from such organizations.

We would like to point out that alternative oil, *trans*-free palm oil, is available much cheaper than hydrogenated vegetable oils, and the industry people may have advocated the shift from *trans* fat to palm oil using the cholesterol hypothesis. However, palm oil is not a safe vegetable oil as explained above. The Japanese administration appears to have approved the use of “vegetable fat or edible fat” instead of “palm oil” for labeling packaged foods because palm oil had previously been used only for industrial purposes,

e.g., soap production. Currently, palm oil holds the second position among vegetable fats and oils consumed in Japan, the number one being canola oil (>40% of the total). Consumers cannot tell what kind of fats and oils are included in packaged foods when edible oil or vegetable oil is approved for labeling. Another intentional (or unintentional) aspect of industrial *trans* fat bashing is associated with double-low rapeseed oil. Linking the industrial *trans* fats only to LDL-C/HDL-C and CVD, the problems of adverse activities of some other vegetable oils were probably expected to be ignored by critical eyes.

IV-3. Double-low rapeseed oil - disregarded or hidden toxicity

A cultivar of rapeseed low in toxic erucic acid and glucosinolates was established in around 1986, and its cultivation area was increased in the central area of EU, then increased death of wild rabbit and roe deer was noted. The European Commission restricted the cultivation area of the double-low variety (Schmid A, 1992). Another step taken worldwide was to set the upper limit of rape meal to be fed to livestock. However, no other regulations appear to have been issued worldwide.

The toxic substance(s) in canola oil is hexane-soluble, hence the effects may not be confined to herbivores. In fact, the toxic effects were observed in many organs of rats and boars as explained above, although the active component(s) has not been identified. It happened to us that both canola oil and hydrogenated soybean oil exert their toxicity at least partly through inhibition of vitamin K₂-dependent processes as dihydro-vitamin K₁ does (Hashimoto Y, 2014). In a DNA microarray analysis, the genes that were up- or down-regulated by canola oil and hydrogenated soybean oil, as compared with soybean oil, agreed >90% in the rat testis.

One of toxic activities of canola is endocrine disturbance and we are surrounded by vegetable oils with environmental hormone activities (Fig. 17). Japanese are particularly in danger of endocrine disturbing oils (Iwamoto T, 2006; Anderson A-M, 2008), because vegetable oils/animal fats ratio of ingested foods is high and canola oil and vegetable fats and oils with similar activities comprises the major parts of all fats and oils. Behavioral changes, altered development of sexual characteristics, and increased neuronal disorders, if it is occurring in Japan, are suspected to be associated with lipid nutrition.

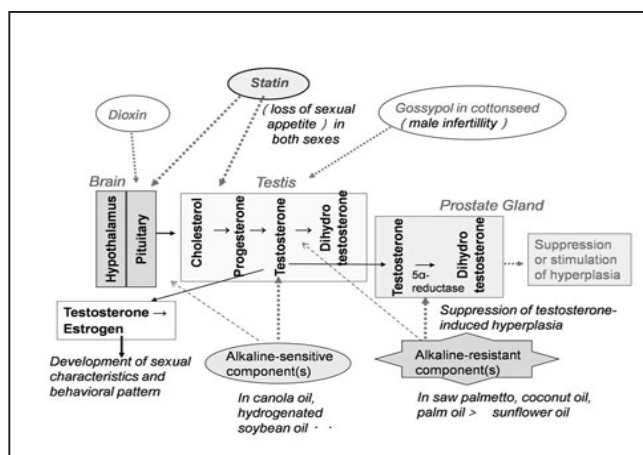


FIGURE 17 Environmental Endocrine Disturbing Substances

Alkaline-sensitive component(s) (vitamin K₂-inhibiting) is presumed to be present in canola and some other vegetable oils. Alkaline-resistant component(s) in some tropical fats is known as inhibitor(s) of 5 α -reductase to form dihydroxy testosterone.

IV -4. Codex General Standard for the Labelling of Prepackaged Foods - FAO/WHO, 2010

According to this standard, fats and oils are classified by the difference in melting points as usual, and each is classified into animal and vegetable. “Partially hydrogenated” is used as appropriate, and animal fats are to be defined as pork fat, lard or beef fat.

This classification is apparently rational but all types of vegetable oils can be labeled solely as “vegetable oil”, regardless of the difference in the fatty acid and minor component compositions. As pointed out by us and many other scientists (Table 2), differential physiological and nutritional effects have been reported for different vegetable oils. It cannot be a simple mistake of the Codex committee to disregard all these adverse effects of some types of vegetable oils (Table 2), and here we feel the presence of intentional tactics of the food industry. We propose that labelling the type of vegetable oils is essential for consumers to choose foods.

Concluding remarks

Cholesterol hypothesis has been examined by randomized, controlled trials (RCT) to reveal that raising the polyunsaturated/saturated ratio of ingested foods and reducing cholesterol intake are rather detrimental for the prevention

of CVD and reduction of all-cause mortality. Observational clinical studies as well as basic studies that are consistent with this interpretation have been reported. Interestingly, some vegetable fats and oils share a common mechanism with statins and warfarin to disturb tissue vitamin K₂-dependent processes, and osteocalcin-regulated functions of various organs. Thus, vegetable oils with high ω -6/ ω -3 ratios and vegetable fats and oils with stroke-stimulating activities were proposed to be causatives of CVD, diabetes, kidney disease and other lifestyle-related diseases; dietary cholesterol and animal fats are evaluated to be relatively safe.

Based on these observations and interpretations, we propose that most lipid nutritional guidelines from authoritative organizations should be reevaluated simply based on available evidence and without disregarding reports demonstrating adverse effects.

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Chapter Six

Why The Lipid Hypothesis Of Coronary Heart Disease Is Fallacious And Dangerous

Paul J. Rosch, MD, Uffe Ravnskov, MD, PhD

Not everything that can be counted counts, and not everything that counts can be counted.

– Albert Einstein

Abstract

The lipid hypothesis postulates that decreasing blood cholesterol significantly reduces future coronary events. It is based on experiments showing that feeding saturated fat and cholesterol to rabbits raised cholesterol and produced fatty arterial deposits similar to those seen in people. Subsequent support seemingly came from epidemiologic studies showing a correlation between saturated fat, cholesterol levels and deaths due to CHD (coronary heart disease), but after scrutinizing these reports, they appeared to be heavily biased. Furthermore, trials to lower cholesterol by restricting saturated fat not only failed, but some reported an increase in coronary deaths. Cardioprotection from reducing cholesterol and LDL levels due to statin therapy was demonstrated in men with existing coronary disease, but it is now apparent that this and other alleged benefits result from pleiotropic effects unrelated to lipid lowering. In addition, there are growing concerns about significant side effects that have been suppressed in drug company sponsored studies or are starting to surface with long-term follow-up.

How The Cholesterol Hypothesis Of Coronary Atherosclerosis Originated

Cholesterol crystals were first identified in bile and gallstones by the French physician and chemist François Poulletier de la Salle around 1769¹.

Towards the end of the century, Antoine Francois de Fourcroy found these crystals to be identical to those obtained from adipocere, a waxy material in the fat of putrefied corpses.² In 1815, Michel Eugène Chevreul isolated and purified the crystallized material from gallstones and named it cholesterin, from the Greek *chol* for bile plus *stereos* for solid.³ This was changed to cholesterol when it was subsequently found to be a sterol, and the chemical suffix *ol* for alcohol was added⁴. M.F. Boudet confirmed the presence of cholesterol in human blood in 1833⁵, and ten years later, J. Vogel suggested that cholesterol was present in arterial plaque⁶.

The term atheroma, from the Greek *ather* (gruel or paste) and *oma* (lump) had been coined by the Swiss physiologist Albrecht von Haller in his 1755 monograph, *Opuscula Pathologica* to describe arterial plaque with a yellowish pustular core that was more common in the elderly⁷. In 1856, the renowned pathologist Rudolph Virchow confirmed that atheroma were age related and was the first to demonstrate that atherosclerotic plaque contained cholesterol^{8a}. However, he did not believe that cholesterol caused plaque, which he referred to as *endarteritis deformans* to emphasize it resulted from an irritative process that injured the intimal lining of arteries. The cholesterol deposits came later.

Virchow's celebrated contemporary, Karl Rokitansky, also described inflammatory cells in atheroma, but believed they came from healing and resorption of thrombi rather than inflammation⁹. Felix Marchand, another German pathologist, coined the term atherosclerosis, from the Greek *sclerosis* (hard) in 1904 to describe a hardening process of atheroma that started in the inner lining of arteries¹⁰. This was to distinguish it from arteriosclerosis, (hardening of the arteries), which had been introduced in 1829 by the French pathologist Jean Lobstein to describe stiffening and thickness of the arteries¹¹. Arteriosclerosis was thought to be due to a loss of elasticity in the muscular portion of the artery with aging that was often associated with calcification¹². However, since calcification of atheroma also occurs, atherosclerosis and arteriosclerosis were often viewed as synonyms and are still often used interchangeably.

There was relatively little concern about either condition since CHD was not a significant problem, and prior to 1920, less than 10% of all deaths were due to heart disease. Most likely the reason was that the disease CHD

was unknown to most doctors and they therefore put another diagnosis on the death certificate. Up to the early seventies CHD mortality increased steadily, but part of the increase was probably the introduction of ECG in the thirties and of aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) in the sixties allowing a more correct diagnosis in many patients. However, the increasing use of hydrogenated fatty acids in margarine may have played a role.

Interest in the role of cholesterol began when there were a series of mysterious deaths in a Russian battalion during the early 20th century war with Japan. It was investigated by A. I. Ignatowski, Professor of Medicine at the Imperial Military Medical Academy in St. Petersburg, who determined it was due to a shipment of polluted meat. To prove this, he fed tainted meat to rabbits, and although none died, autopsies revealed an increase in fatty deposits in several arteries¹³. He thought this was consistent with the theory of Ilya Mechnikov, a Nobel Prize recipient who had previously proposed that an excess of dietary protein accelerated hardening of the arteries and other aspects of the aging process. Ignatowski fed rabbits a protein rich diet of meat, egg and milk that caused cholesterol deposits in the aorta reminiscent of atherosclerotic plaque in people that seemed to confirm Mechnikov's "protein toxicity" theory and published his findings in 1909¹⁴.

The following year, Adolph Windaus, a German physician and chemist, who later received a Nobel Prize, reported that atheroma in human aortas contained 6 times more free cholesterol than healthy arteries, and over 20 times more cholesterol ester¹⁵. These observations made a great impression on Nikolai Anitschkow, who had just graduated from the same St. Petersburg Military Medical Academy. He suspected that it was cholesterol and fat rather than protein in the diet that caused these atheromatous lesions, and with the assistance of Semen Chatalov, a medical student at the Academy, he showed that simply feeding rabbits purified cholesterol obtained from egg yolks dissolved in corn oil could reproduce the identical changes Ignatowski described¹⁶. In their 1913 paper, they reported that the earliest lesions appeared in the aortic arch and had vacuolated cells containing cholesterol¹⁷.

However, Anitschkow's research was relatively unknown to Western

scientists until he published an English review of the issue in 1933¹⁸. Nor did this attract much attention until 1950, when John Gofman emphasized the importance of Anitschkow's discovery that feeding cholesterol to rabbits promptly led to atherosclerosis. Gofman and coworkers utilized a powerful ultracentrifuge to analyze the hypercholesteremic serum samples of their cholesterol-fed rabbits and identified two distinct layers or compartments. One that was located at the top of the serum sample was designated low-density lipoprotein cholesterol (LDL) and the fraction deposited at the bottom of the test tube was called high-density lipoprotein cholesterol (HDL)^{19,20}. They also claimed that LDL was responsible for the rapid progression of atherosclerosis in human beings. This precipitated an avalanche of studies, including the research of Michael Brown and Joseph L. Goldstein that led to the development of statins and a Nobel Prize "for their discoveries concerning the regulation of cholesterol metabolism"²¹.

In a 1958 editorial, Dr. William Dock, a renowned cardiologist who was then Chairman of the Department of Pathology at Stanford University Medical School, wrote in an editorial, "Thus the early work of Anichkov bears comparison with that of Harvey on the circulation and of Lavoisier on the respiratory exchange of oxygen and carbon dioxide"²². Dock also compared the significance of Anitschkow's research to Koch's discovery of the tubercle bacillus. And a recent ranking of "Cardiology's Ten Greatest 20th Century Discoveries" listed the top three as 1) The Electrocardiogram, 2) Preventive Cardiology and the Framingham Study, 3) The "Lipid Hypotheses" and Atherosclerosis²³. Small wonder that those who dispute the dangers of cholesterol and the panacea-like properties of statins have a steep uphill battle against powerful adversaries who are intent on preserving their profits by perpetuating this dogma.

The Lipid Hypothesis

Note that the above authors used the term "Lipid Hypotheses", which implies that there was more than one such theory of the etiology of atherosclerosis. This is not surprising since by the 21st century, the lipid hypothesis was often confused with the diet-heart hypothesis or was referred to as "the cholesterol controversy"²⁴. The term "lipid hypothesis"

had also been used earlier by Steinberg and others, but came into common usage following a 1976 paper by E.H. “Pete” Ahrens Jr. from Rockefeller University’s Center for Prevention of Premature Arteriosclerosis²⁵. He defined the lipid hypothesis as follows:

The Lipid Hypothesis is the postulate, based on Framingham and similarly derived data, that reducing the level of plasma cholesterol in an individual or in a population group will lead to a reduction in the risk of suffering a new event of coronary heart disease. It is a premise based on the undisputed fact that people with higher plasma cholesterol levels have more and earlier coronary heart disease than do those with lower cholesterol levels; but the premise has not yet been proved true to the satisfaction of epidemiologists and biostatisticians or of the medical community at large. The Lipid Hypothesis, then, is simply an inference derived from accepted facts; though the hypothesis has been put to the test repeatedly in the past two decades, completely satisfactory evidence has not yet been advanced either pro or con.

Ahrens emphasized that this statistical association did not prove that cholesterol caused heart disease and that the lowering of cholesterol was a relative rather than an absolute risk reduction.

The Diet-Heart Idea

The “diet-heart” concept probably originated from a study published in 1953 by Ancel Keys, the director of the Laboratory of Physiological Hygiene at the University of Minnesota. According to Keys, fat food was the culprit. His proof was a diagram, which showed that the intake of fat food and the death rates from CHD followed each other closely in six countries. The six points on the diagram lay as on a string with Japan at the lower left corner and the US in the upper right²⁶. However, as pointed out by Yerushalmy and Hilleboe four years later²⁷, data were available from 22 countries at that time, and if all the data were included, the strong association disappeared.

But Keys returned with a new study named Seven Countries²⁸. In cooperation with local doctors, scientists and health authorities he selected sixteen local populations in the Netherlands, Yugoslavia, Finland, Japan, Greece, Italy and the US. Men between the age of 40 and 59 were studied and anything, which might conceivably cause CHD, was investigated. The men were followed for about five years, and all heart symptoms and all

deaths were recorded. In his previous study he claimed that the intake of total fat was important, but in this new study, no association was found between the total fat intake and CHD. Instead his conclusion from this gigantic project was that what best predicted the number of heart attacks was how much animal fat people ate. Heart attacks were common in countries where people ate considerable amounts of animal fat, whereas they were rare in countries where intake was much lower.

However, many contradictory findings were ignored. For instance, CHD mortality was three times more common in eastern than in western Finland, although the difference between the intake of saturated fat in each area was minimal. In Greece, CHD mortality was 6-7 times higher on the island Corfu than on Crete although their intake of saturated fat was also identical; if anything, it was a little higher on Crete. Furthermore, including all 16 districts, intake of saturated fat was weakly related to CHD mortality but not to major ECG abnormalities at entry. The latter observation is evidently more relevant because whereas local doctors wrote the death certificates, American experts evaluated the ECG findings. In spite of these obvious biases, the study was widely heralded as the definitive proof of a causal link between SFA (saturated fat) intake and CHD. As Keys triumphantly proclaimed, “No other variable in the mode of life besides the fat calories in the diet is known which shows such a constant relationship to the mortality rate from coronary or degenerative disease.”

Using intricate mathematical manipulations of laboratory study results - including his own - Keys created a formula to predict what happens to cholesterol levels when people eat different types of diets. According to his complicated formula, cholesterol goes up if you eat saturated fat and goes down if you consume a lot of polyunsaturated fat, the dominating fat in most vegetables oils²⁹.

It is simply impossible to draw any valid conclusions from Keys' studies and many observational studies have also shown that neither dietary cholesterol or saturated fat cause high cholesterol. For instance, males in some African tribes who consumed twice as much saturated fat as their counterparts in other countries had the lowest cholesterol levels ever seen in healthy people, and heart disease was rare^{30a}. Furthermore, no study has found an association between the intake of dietary cholesterol and its level

in the blood^{30b,31}.

Raymond Reiser, an American professor in biochemistry, was the first to question the association between saturated fat and cholesterol based on a thorough review of 40 trials^{32a}. He pointed out several types of methodological and interpretational errors: For instance, instead of natural saturated fat, many authors had used vegetable oils saturated by hydrogenation, a process that also produces trans fatty acids. We now know that trans fatty acids indeed cause cholesterol levels to go rise, and that trans fats can cause CHD. Furthermore, few researchers have looked at saturated fat intake as the only variable. If they changed the intake of saturated fat, they also changed the intake of monounsaturated or polyunsaturated fats, or both, mostly in the opposite direction. Russell Smith, a psychologist and statistician, who later reviewed over 2,000 studies on the link between dietary fat and cholesterol, was particularly critical³³:

The word “landmark” has often been used to describe Ancel Keys Seven Countries Study, commonly cited as proof that the American diet is atherogenic. The dietary assessment methodology was highly inconsistent across cohorts and thoroughly suspect. In addition, careful examination of the death rates and associations between diet and death rates reveal a massive set of inconsistencies and contradictions..It is almost inconceivable that the Seven Countries study was performed with such scientific abandon. It is also dumbfounding how the NHLBI/AHA alliance ignored such sloppiness in their many “rave reviews” of the study... In summary, the diet-CHD relationship reported for the Seven Countries study cannot be taken seriously by the objective and critical scientist”.

The Arguments for the Diet-Heart Idea

There was not much interest in cholesterol until the 1950's when CHD became the leading cause of death in the U.S. Due to Ancel Keys' studies it was widely assumed that elevated cholesterol was the culprit. Further support came from the Framingham study based on a 6-year follow-up analysis of over 4,000 healthy men and women aged 31-65. They found that serum cholesterol measured at the start was significantly higher among those who had suffered from CHD during the observation period³⁴. This was reinforced by the 1977 McGovern Senate Committee on Nutrition report that focused on avoiding saturated fats to lower cholesterol levels³⁵.

The problem was that the Prudent Diet and other attempts to lower heart attack risk by following these recommendations were embarrassing failures. No dietary experiment had been able to reduce heart mortality by avoiding saturated fat^{32b,36a}. Even when combined with other cardioprotective lifestyle-changing measures the diet was ineffective.

One of them was the Multiple Risk Factor Intervention Trial (MRFIT). This was a randomized primary prevention trial funded by the National Heart and Lung Institute to test whether multiple risk factor intervention would prevent deaths from CHD in high-risk men³⁷. Over 360,000 asymptomatic men aged 35-57 were screened to select those in the top 15% of potentially modifiable risk factors based on Framingham equations. Almost 13,000 with no history or evidence of heart disease were recruited and half of them were given dietary recommendations to lower blood cholesterol, antihypertensive drugs to lower blood pressure, and counseling for exercising and cigarette smoking cessation. The other half was referred to their usual source of medical care. However, as described in chapter 7, it was a gigantic failure. No benefit was achieved, although their intake of cholesterol was halved and their intake of saturated fat was lowered by 25%, no benefit was achieved.³⁸

That a reduction of saturated fat is meaningless also appears to be confirmed by two major observational studies. The World Health Organization's Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) epidemiologic project was undoubtedly the largest study ever designed to explore the relationship between "risk factors" and cardiovascular disease³⁹. It began in 1971 as a collaborative effort involving thirty-two centers in twenty-one countries that monitored approximately ten million men and women aged 25-64 for ten years.

The MONICA study also failed to find a link between Framingham risk factors and CHD mortality, and it thoroughly debunked the diet-heart hypothesis. All the countries in the top eight for saturated fat consumption had lower death rates for heart disease than all of the eight countries that consumed the least fat. For example, the French consumed three times as much saturated fat compared to Azerbaijan but had one-eighth the rate of heart disease deaths. Heart disease mortality in Finland was four times greater than in Switzerland, even though saturated fat consumption was

similar. Researchers noted a significant rise and subsequent fall in coronary death rates over the past five decades that could not be explained, but there was again no correlation with changes in diet or Framingham risk factors of cholesterol, hypertension and smoking.

Most physicians are familiar with the Framingham and Seven Countries Study, but few are aware of MONICA, although it is far and away the largest study of its kind. In meta-analyses involving data for some sixty-two other prospective epidemiological studies, the combined total number of pooled subjects was 1.24 million. MONICA had eight times more but its data was not included based on arbitrary eligibility criteria established by the authors.

The other major study with contradictory results was the Women's Health Initiative (WHI) study in 1991 established by NIH to address the most common causes of death, disability and impaired quality of life in postmenopausal women. It was a 15-year multi-million-dollar project involving 161,808 healthy postmenopausal women and 40 clinical centers. Its focus was on strategies to prevent heart disease, breast and colorectal cancers by observational studies and the following three interventional clinical trials; Hormone Therapy, Calcium/Vitamin D and Dietary Modification. The Dietary Modification component evaluated the effect of a low-fat and high fruit, vegetable and grain diet on the prevention of CHD, breast and colorectal cancers. Study participants followed either their usual eating habits or the dietary regimen noted above. The results indicated that despite some reduction in cardiovascular risk factors such as blood lipids and diastolic blood pressure, there was no significant reduction in the risk of CHD or stroke in the cohort that restricted fat and increased fruit, vegetables and grain^{40,41}.

The Arguments for the Lipid Hypothesis

From the beginning researchers were frustrated by their inability to find a natural product or drug to reduce cholesterol levels. The cholesterol-lowering properties of nicotinic acid (Vitamin B3) were discovered in 1955 but the drug was ineffective in preventing fatal heart disease and the side effects were intolerable.

Triparanol (MER/29), an amine compound approved in 1959, was the

first drug that inhibited cholesterol synthesis⁴², but in contrast to statins, it blocked enzymes at the final stages of synthesis. However, it was withdrawn 3 years later because of skin lesions, impotence, cataracts, neuropathy and other serious side effects⁴³. Not unexpectedly, the same side effects have been described after statin treatment as well. Probucol (Lorelco), an antioxidant, was approved to lower cholesterol in 1982 but was also withdrawn because of side effects and lack of efficacy^{44a}.

Clofibrate, which had been marketed in England since 1958, was approved in the U.S. in 1967 as Atromid-S. Its mechanism of action was not clear, cholesterol-lowering effects were not impressive, and it was discontinued in 2002 because of increased risk of cancer, liver, gall bladder and pancreatic disease^{44b}.

Other more potent and less toxic fibrates such as gemfibrozil (Lopid) and fenofibrate (Tricor) are still available and are primarily used as adjunctive therapy to lower triglycerides and LDL, although none of them have been able to lower heart or total mortality. None of these cholesterol-lowering therapies were popular since they had significant side effects, none of them were able to prevent mortality and there was little proof that they reduced coronary events^{36b,44c}.

A more promising candidate was cholestyramine (Questran), an anion-exchange resin that binds bile acids in the gastrointestinal tract and prevents their reabsorption. As a result, blood cholesterol falls because more of it is converted to bile acids in the liver to replenish their loss. In 1973, the NIH initiated its Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) in 3800 asymptomatic middle-aged men with cholesterol levels over 265 mg/dl that were largely due to an elevated LDL. It was predicted that after 7 years, Questran would lower coronary morbidity and mortality by 50 %^{45,46}. But, as described in chapter 7, this was not the case. The differences in outcome between the two groups were not statistically significant.

Despite this, the results were triumphantly proclaimed as definitive proof of the lipid hypothesis. As a result, The National Cholesterol Education Program was promptly launched, and focused on lowering LDL by diet and drugs to less than 100 mg/dl, cholesterol to under 200 mg/dl, and increasing HDL to 40 mg/dl or higher⁴⁷. These recommendations were soon endorsed

by leading authorities as well as the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation and the American Heart Association. The Centers for Disease Control has issued periodic updates since then identifying additional risk factors and therapies⁴⁸. September was also proclaimed “National Cholesterol Education Month”, during which everyone is urged to obtain a lipid profile.

However, a meta-analysis of the cholesterol-lowering trials published before the introduction of the statins found that they did not lower CHD mortality and that they had increased total mortality^{36c}. Furthermore, the reason for the widespread belief in such trials was that several with a negative outcome had been excluded in the previous meta-analyses^{36d}. Consequently, skepticism about the benefits of cholesterol lowering therapy increased⁴⁹, but this changed with the advent of statins.

In 1994, the Merck trial 4S was published⁵⁰. A total of 4444 men and women with a previous heart attack were treated, half of them with simvastatin, the other half with a placebo. After 5.4 years, 8.5 percent had died from a heart attack in the control group, compared with 5 percent in the treatment group. For the first time a cholesterol lowering trial had succeeded in lowering the risk of both fatal and nonfatal CHD, and even total mortality. The results were heralded in the British Medical Journal: “Lower patients’ cholesterol now! There is no longer any doubt about the benefit and safety of treating hypercholesterolemia in patients who have had a myocardial infarction.”

However, the improvement included men only; the number of women who had died from a heart attack was in fact higher in the statin group, although not with statistical significance. Furthermore, none of the numerous statin trials that have been published later have succeeded in lowering CHD mortality to that extent; at most it has been lowered by 2 %.

Few are aware that in 1991, Merck had already published EXCEL, the first primary-preventive statin trial⁵¹, but as can be seen in chapter 7, it was a complete failure. In fact, no primary-preventive statin trial has ever succeeded in prolonging the life for the participants, and no trial, whether primary or secondary preventive, has succeeded with that for women. There is also a serious problem with statin treatment. All authors have claimed that adverse effects are mild and rare, but as detailed in other chapters, this

is very far from the truth.

Everyone is entitled to their own opinions and theories, but not their own facts. And the facts are that the conclusions based on all the studies cited above are erroneous. The cholesterol feeding studies were done in rabbits, which are herbivorous, and dietary cholesterol is foreign to them. When these experiments were repeated in rats and baboons, no atherosclerotic lesions were produced, and no study has found any association between the intake of saturated fats and degree of atherosclerosis in man^{30c}. What is also ignored is the result from the 30-year follow-up of the participants in the Framingham study. What the authors found was that for each 1 % drop in cholesterol, there was actually an 11 % **increase** in coronary and total mortality⁵².

Some of the cholesterol-lowering trials succeeded in preventing various types of nonfatal cardiovascular events, but at the expense of numerous significant side effects, and as mentioned above, several trials with a negative outcome were excluded from the reviews.

Why Measuring Cholesterol and LDL Is A Waste Of Time And Money

The NIH, American Heart Association and other authorities constantly advise everyone from children to the elderly of the importance of knowing your “cholesterol numbers”. Lipid theory proponents still maintain that coronary atherosclerosis is initiated when LDL infiltrates and accumulates in the intima of vessels and activates the endothelium to attract leukocyte adhesion molecules and chemokines^{53,54}. The fact is that several observational studies have shown that high total or LDL-cholesterol is not a risk factor for CHD^{55,56,57,58,59,60} and that on average these values are lower than normal in patients with acute CHD.⁶¹

Many studies have also shown that high cholesterol is not a risk factor for senior citizens; in fact, at least 19 studies have shown that old people with high LDL-cholesterol live the longest⁶². No association between cholesterol levels and the degree of atherosclerosis has ever been found in postmortem studies of the general population either, and no clinical or imaging study has found any relation between the degree of cholesterol lowering and improvement⁶³. Moreover, at least nine studies of people with familial

hypercholesterolemia (FH) have shown that LDL-cholesterol in those with heart disease is not significantly higher than in those without^{64,65,66,67,68,69,70,71,72}, and the cerebral arteries of people with homozygotic FH are not more atherosclerotic than those of other people⁷³. Most likely, CHD in people with FH is caused by an increased level of various coagulation factors, some of which have also been inherited.^{74,75,76,77,78,79,80,81}

So why bother measuring total or LDL-cholesterol? Their benefit in patients with existing heart disease is most likely due to immunomodulatory, anti-inflammatory, anticoagulant and other diverse pleiotropic effects. As a result, statin therapy guidelines have abandoned lowering LDL as a goal and replaced it with an arbitrary 10-year risk assessment that would make tens of millions of additional individuals eligible for treatment. These include all diabetics and many healthy people over the age of 50, despite the fact that statins cause diabetes and provide no protection for anyone who does not have CHD.

In that regard, it is important to reemphasize that cholesterol, hypertension, and smoking are not risk “factors”, which implies a causal relationship, but rather risk “markers” that are merely statistical associations. There are hundreds of similar correlations, including a deep earlobe crease, potbelly, premature vertex baldness, or living in Glasgow. All of these are associated with an increased risk for CHD. But that does not mean that plastic surgery, a tummy tuck, hair transplant, or moving to Honolulu will lessen the likelihood of a heart attack.

Inflammation

During the last few years, there has been increased interest in inflammation as a causal factor of atherosclerosis^{82,83}, as expressed below by Dr. Peter Libby, Chief of Cardiovascular Medicine at Brigham and Women’s Hospital, which is affiliated with Harvard Medical School

Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. These new findings provide important links between risk factors and the mechanisms of atherogenesis. Clinical studies have shown that this emerging biology

*of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein, prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors.*⁸⁴

The culprit is described as “low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein”, which has been used to assess the severity of acute inflammation for over 80 years. But what is the nature of this low-grade inflammatory process that does not respond to antibiotics? Virchow was very specific when he wrote:^{8b}

*We cannot help regarding the process as one which has arisen out of irritation of the parts stimulating them to new, formative actions; so far therefore it comes under **our ideas of inflammation**, or at least of those processes which are extremely **nearly allied to inflammation**... We can distinguish a stage of irritation preceding the fatty metamorphosis, comparable to the stage of swelling, cloudiness, and enlargement which we see in other inflamed parts. I have therefore felt no hesitation in siding with the old view in this matter, and in admitting an inflammation of the inner arterial coat to be the starting point of the so-called atheromatous degeneration. (emphasis added)*

Note that Virchow did not believe cholesterol caused atherosclerosis. The initiating factor was irritation and the cholesterol deposits came later. As indicated by the highlighted words, he was careful not to label this irritative process inflammation, because 2,000 years earlier, Celsus had defined inflammation as heat, pain, redness and swelling (*calor, dolor, rubor, and tumor*), to which Virchow later added disturbance of function (*functio laesa*). All of these were acute signs and symptoms that could be seen or felt, such as a pus-filled skin boil. In contrast, this was a chronic, indolent, hidden and silent process whose presence could only be verified by microscopic examination. This was not inflammation as defined by Celsus, but rather some prophlogistic process that had similar elements of swelling and cloudiness.

It has also been proposed that CRP causes coronary atherosclerosis, in addition to being a better risk marker than LDL, as indicated below.

Traditionally, CRP has been thought of as a bystander marker of vascular inflammation, without playing a direct role in the CVD. More recently, accumulating evidence suggest that CRP may have direct proinflammatory effects, which are associated with all stages of atherosclerosis. In our recent

*study, the results demonstrate that monocytes exhibit an enhanced production of interleukin-6 (IL-6) in response to CRP, and this response is significantly inhibited by simvastatin in a dose-dependent manner. This may be of important interest in the connection between CVD and CRP. Based on this evidence, we hypothesize that CRP is not only an inflammatory marker but also a direct cause of CVD, and treatments that reduce CRP should be of benefit for primary and secondary prevention of CVD. Administration of several agents, especially statins has been showed to modify CRP concentrations with a concurrent fall in cardiovascular events. Our clinical investigation suggested that treatment with a single high-dose or a short-term common dose of simvastatin could rapidly reduce CRP level.*⁸⁵

However, the results from the JUPITER trial (see chapter 7) contradict this idea, because although LDL-C was reduced by 50% and CRP was 37% lower in the treatment group, the number of fatal heart attacks was higher⁸⁶.

Moreover, reducing inflammation does not reduce heart disease. The powerful non-steroidal anti-inflammatory drug Vioxx was taken off the market because it caused heart attacks, and other anti-inflammatory drugs have had the same effect⁸⁷. Furthermore, steroids like cortisone are extremely potent anti-inflammatory agents, but are more likely to cause cardiovascular problems than prevent them. Aspirin does have anti-inflammatory effects, but its cardioprotective benefits are more likely due to its antiplatelet and anticoagulant effect. In our view, and as proposed in chapter 11, inflammation can result from infection of the arterial wall.

Despite the trend to replace LDL with CRP as the cause of coronary atherosclerosis, a majority of researchers and physicians still maintain that high LDL is the perpetrator. Many believe this is due to the clout of the Cholesterol Cartel of statin, low fat food and lipid testing equipment manufacturers, who are intent on preserving their profits, and fund and oversee favorable clinical trials and meta-analyses. Most authors of these reviews and the organizations they represent are recipients of largesse from drug companies or have other conflicts of interest. As H.L. Mencken noted, *“It is difficult for a man to understand something when his income depends on not understanding it.”*

Conclusion

The list of observations and experiments that contradict the diet-heart idea and the lipid hypothesis is almost endless and it gets longer every year. In

spite of this the cholesterol lowering campaign has continued uninterrupted along with a growing collection of adverse side effects. Dietary recommendations to replace saturated fat with foods rich in sugar and other carbohydrates have created a worldwide epidemic of obesity and type 2 diabetes. Moreover, millions of additional healthy people are now being urged to take statins that may convert over 20% of them to patients suffering from muscular weakness and pain, diabetes, impotency, various types of cerebral dysfunction, neuropathy, cataract, kidney damage and cancer.

However, there is an increasing recognition among many researchers that saturated fat and dairy products are beneficial and are not the cause of coronary atherosclerosis. Many feel that the new guidelines for statin therapy are a dangerous public health experiment, since they could put millions of healthy people at risk for serious side effects, with no proof they will provide cardiovascular or other benefits. In an article in the December 2014 issue of JAMA-Internal Medicine appropriately entitled “Prevention Guidelines Bad Process, Bad Outcome, Dr. Steven Nissen chairman of the department of cardiovascular medicine at the Cleveland Clinic, former president of the American College of Cardiology, and a leading researcher and staunch advocate of statin therapy, wrote *“The ACC and AHA should promptly revise the guidelines to address the criticisms offered by independent authorities”*⁸⁸.

With respect to the future, it is not likely that the lipid hypothesis will fade away. Although trials showing that drugs designed to raise HDL (the “good cholesterol”) had to be halted due to increased cardiac mortality, this is still being pursued. Scientists recently created a synthetic molecule that “mimics” HDL and allegedly reduces plaque buildup in mice.⁸⁹ There is also continued interest in cholesterylester transfer protein (CETP) inhibitors, some of which have effects on both LDL and HDL⁹⁰ as discussed in chapter 1. And despite the irrelevance of lipid levels, monoclonal antibodies to lower LDL are being developed for patients on statins who have not obtained optimal benefits. These PCSK9 inhibitors are given by injection every 2 to 4 weeks, with an anticipated initial cost of \$6,000 to \$7000/year.⁹¹

The preliminary results from PCSK9 inhibitor trials were not

encouraging. These trials have been too short (11 months in an evolocumab trial⁹² and 80 weeks in an alirocumab trial)⁹³. In addition, 7% and 30% respectively, discontinued anti-PCSK9 therapy. Although these drugs lower cholesterol more than 50%, any benefits were minimal. In the evolocumab trial the absolute benefit as regards CVD and unknown mortality was 0.1% and there was no benefit at all with respect to acute myocardial infarction and stroke. In the alirocumab trial the absolute benefit for CHD and unknown mortality was 0.6%, and fatal or nonfatal ischemic stroke occurred more often in the treatment group (0.6% vs. 0.3%). Nevertheless, both drugs were recently approved and are being hyped in deceptive ads, as noted in Chapter 1.

It would be wise to heed the adage that *“Those who do not learn from the mistakes of history are doomed to repeat them”*. With regard to the iconoclastic opinions expressed in this paper, we would remind the reader of Arthur Schopenhauer’s contention, *“All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident”*, as well as Max Planck’s observation, *“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.”* Only time will tell if this will be the fate of the lipid hypothesis.

Key Issues

- No study of unselected individuals has found any association between total or LDL-cholesterol and the degree of atherosclerosis
- No study has documented that a high intake of cholesterol influences its serum level
- Almost all observational studies have shown that a high intake of saturated fat does not raise cholesterol
- Laboratory experiments concerning the effect of dietary lipids on blood lipids are biased
- All cohort and case-control studies have found lack of an association

between a high intake of saturated fat and CHD

- No dietary trial has succeeded in lowering CHD mortality by reducing the intake of saturated fat
- Many studies have shown that high t-C or LDL-C is not a risk factor for middle-aged and elderly people
- All studies have shown that high cholesterol is not a risk factor for women
- Before the introduction of the statins, no cholesterol-lowering drug trial has succeeded in prolonging the life for the participants.
- The statins have only been able to lower heart mortality in people with heart disease and the effect is minimal
- As no cholesterol-lowering trial has found a dose-related exposure-response, the small benefit from statin treatment must depend on other effects
- The small benefit from statin treatment is outweighed by their many serious adverse effects
- There is no clinical evidence that, the new cholesterol-lowering drugs the PCSK9-inhibitors are able to lower the risk of CVD.

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Chapter Seven

Historical Perspective on the Use of Deceptive Methods in the War on Cholesterol

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Abstract

For over half a century dietary and pharmacological approaches aimed at preventing cardiovascular disease (CVD) have mainly been based on the hypothesis that elevated cholesterol is atherogenic and that its lowering with diet or drugs will reduce the degree of atherosclerosis and the risk of CVD. We have reviewed the literature on this topic and have found numerous ways by which the supporters of this hypothesis have succeeded in misleading the readers. In fact, an abundant number of studies have shown that the cholesterol hypothesis is unable to satisfy any of Bradford Hill's criteria for causation. We have also described how the directors of the clinical trials have succeeded in minimizing the pervasiveness of the adverse effects of statin treatment. Overall, the half century long war on cholesterol has been counterproductive because the financial victory for food and drug companies in attacking cholesterol has come at the cost of impaired health for the masse.

Introduction

The reputed role of high serum cholesterol as a risk factor in CVD has been a source of controversy and debate for decades. This debate has been described as a war between the advocates, who view high cholesterol as a causal agent in coronary heart disease (CHD)^{1,2} against the skeptics, who consider cholesterol a vital component of cell metabolism which is not atherogenic^{3,4,5,6,7,8,9,10,11}. The advocates' main thesis is based primarily on three components: 1) the presence of cholesterol in atherosclerotic tissue; 2) an association between high levels of serum cholesterol and CHD; and 3)

cholesterol-lowering trials with drugs that appear to lower the risk of cardiovascular disease (CVD). Skeptics, by contrast, have emphasized that the advocates have failed to demonstrate evidence of a causal link between cholesterol and CHD. Moreover, as we describe in this chapter, the appearance of an improvement in CVD outcomes with cholesterol reduction is an illusion, one created by the directors of the trials using deceptive statistical means.

An absence of an association between cholesterol levels and the degree of atherosclerosis was first described in 1936¹², a finding which has been confirmed in numerous contemporary studies^{13a}. The fact is that elderly adults with low levels of cholesterol are just as atherosclerotic as those with high levels. That high cholesterol is not a risk factor for CHD has been documented in many studies on a broad range of groups, including women, Canadian men, Swedes, Maoris, elderly people and patients with CHD¹⁴. In a meta-analysis of nineteen studies that included about 68,000 senior citizens that analyzed the relationship between LDL and mortality, those with the highest values lived the longest.¹⁵ Finally, despite claims that statins produce dramatic improvements in CVD outcomes, the effects of statin treatment at a population level is actually quite miniscule. In fact, any beneficial effects of statins are more likely a result of pleiotropic effects, rather than cholesterol lowering¹⁶, because no trial has shown an association between the degree of cholesterol-lowering and the magnitude of beneficial outcomes^{13b}.

Despite the largely disappointing findings from 50 years of cholesterol lower trials, the indictment and conviction of cholesterol as the causal agent in CVD has stood the test of time. In this chapter we have rigorously assessed a broad range of research which has targeted cholesterol reduction with dietary or pharmacological approaches as a means with which to improve cardiovascular health and increase longevity. We have thoroughly evaluated the methodology and findings in this area of research and have reached the conclusion that the grand effort to reduce cholesterol as a strategy to improve health has failed.

The Dietary Trials

It is a fact that an exchange of saturated fat (SFA) with polyunsaturated fatty acids (PUFA) can lower serum cholesterol. This finding has led many researchers to assume that exchanging animal fat for vegetable oil consumption will therefore lower the risk of CHD. Few seem to realize that the reduction of serum cholesterol levels is actually caused by the increased intake of omega-6 PUFA and not by the decrease of the intake of SFA. In accordance, several trials in which a diet rich in SFA was compared with a diet where SFA had been exchanged with food rich in omega-6 PUFA, such as soybean or corn oil, provided findings, which did not support the cholesterol hypothesis.

In the first trial published in 1965 by Rose et al.¹⁷, a diet high in PUFA (corn oil supplementation) produced the goal of a significant reduction of serum cholesterol levels, and yet, resulted in a higher CHD and total mortality in the treatment group. In six similar trials mortality was either higher in the diet group, or no difference was seen between the intervention and control groups¹⁸.

A trial by Dayton et al, which included 800 male war veterans at a nursing home, appeared to have produced a positive result. After seven years a slightly smaller number of those who had consumed the soybean oil diet had died from CHD, but the lower number of CHD deaths was offset by a higher number of cancer deaths. Moreover, although serum cholesterol had been lowered in the treatment group, there was no difference between the degrees of atherosclerosis in the two groups. In fact, those who had consumed the soybean diet, had more cholesterol in the aorta than those who had administered the nursing home's standard fare. In addition, what is often not mentioned in reviews of this study is that there were significantly more heavy smokers in the control group¹⁹.

The Finnish Mental Hospital Trial is one of the most often cited dietary trials in support of the assertion that there are benefits to reducing saturated fat²⁰. About 700 middle-aged male patients were studied at two mental hospitals in Finland. At one of them the patients were given a diet low in saturated fat and cholesterol and high in polyunsaturated fat; at the other hospital they were given the usual hospital diet. Six years later the diets were reversed and the trial continued for another six years. During the trial some of the patients dropped out, and after the first six years the oldest

patients in both groups were exchanged with younger patients. Furthermore, there were considerably more smokers, more who had high blood pressure, and more who were treated with drugs in the control groups.

During both periods there were fewer heart events in the diet group, but with one exception the differences were not statistically significant. It is notable that the almost complete absence of significant effects occurred despite the fact that the authors had used a less demanding method to assess significance, the one-tailed t-test. Ultimately, however, how could they know whether the number of heart attacks in the second period was a consequence of the diet the patients had consumed during the first six year period, or whether it was the result of their present diet?

It is abundantly clear that this trial was terribly flawed. It was neither randomised, nor blinded, and what is not widely known is, that it included female patients, as well. In that part of the trial, published four years later²¹, there was no benefit at all, although the cholesterol levels in the women were reduced even more than in the men. Nevertheless, the authors' conclusion was that *although the observed changes in CHD incidence fall short in attaining conventional criteria of statistical significance, the results of our trial support the idea that among female populations, as well as male, the use of a diet low in saturated fats and cholesterol and relatively high in polyunsaturated fats, exerts a preventive effect upon coronary heart disease.*

MRFIT. Many researchers thought that an intervention limited to a low-fat diet, alone, was not sufficient to improve CVD outcomes. Therefore several multifactorial trials were performed. One of them was the Multiple Risk Factor Intervention Trial (MRFIT); the largest and probably the most expensive cholesterol-lowering trial²². After a routine investigation of more than 360,000 middle-aged men, the researchers selected about 12,000 who were considered especially prone to get a heart attack. The subjects were randomly assigned to two groups of equal size. Those in the treatment group and their families were taught how to avoid cholesterol and saturated fat and increase the intake of polyunsaturated fat and how to quit smoking. High blood pressure was treated energetically, and subjects with weight problems were taught how to reduce calories and get more exercise.

Seven years later blood pressure had been lowered considerably and

many had quit smoking. But their cholesterol levels had decreased by only seven per cent and it had decreased in the control group as well, so the difference between the two groups was only two per cent. Other risk factors had changed in the control group as well. The only difference worth mentioning was that significantly more of the control subjects continued to smoke. The outcome of this trial was not impressive; CHD mortality was non-significantly lower in the treatment group (115 vs 124) and total mortality was a little higher (265 vs 260).

With statistical manipulation, the directors of the study improved the appearance of the findings. The participants were divided into smaller groups, and by excluding a subgroup with a particularly poor outcome, the overall result was better. Almost all the other subgroups had fewer fatal heart attacks. Therefore the trial directors concluded that the intervention program might have had a favorable effect for most of the participants. If some of the men had more heart attacks, it was because of the drugs used to lower blood pressure (although in another subgroup treated with such drugs, the outcome was better). It was also obvious that the outcome was favorable for those who had quit smoking. In fact, the change in smoking habits explained the whole difference.

But the investigators claimed that the figures proved the benefit of lowering blood cholesterol. More prudent diet-heart supporters acknowledge that MRFIT was a failure, but they usually add that the failure occurred because a two percentage lowering of blood cholesterol is too small to have any effect. But with this objection diet was declared worthless as a preventive measure, because the subjects in the treatment group had almost halved their intake of cholesterol, they had lowered their intake of saturated fat by more than 25 per cent, and they had eaten 33 per cent more polyunsaturated fat, whereas the diet was practically unchanged in the placebo group²³.

Overall, dietary trials restricting SFA with increased PUFA has been a disappointment to the advocates of the cholesterol hypothesis. This limitation of diet to improve CVD outcomes has provided the impetus to drug trials to more directly target cholesterol reduction. In the next section we have described how this approach, as well, has been a dismal failure.

Drug Trials in the Pre-Statins Era

Before the introduction of the statins, several cholesterol-lowering drugs were tested, all of them with unimpressive results. The following is a review and analysis of a subset of these trials, including an assessment of how their directors misled the public in producing consensus statements on the effectiveness of cholesterol lowering, when indeed the actual findings were anaemic in their outcomes.

The Upjohn trial. One of them, colestipol, a bile-acid sequestering resin, was used in a randomized, placebo-controlled trial, which was directed by Albert E. Dorr from the Department of Biostatistics at the Upjohn Company. This trial included 2278 hypercholesterolemic men and women from 108 clinics in the US. About half of the participants had been diagnosed with CVD and/or diabetes²⁴. Clinical information about the participants were telephoned to the staff on Upjohn, who made the random assignment. After up to three years of treatment (no information about the mean duration of the trial was given in the report), where cholesterol was lowered by about 15% in the treatment group, 22 men (4.6%) had died in the placebo group, but only nine (1.6%) in the colestipol group, whereas no difference was seen among the women (no figures were given). The data showed however, that the placebo-group must have included more patients with familial hypercholesterolemia, because triglycerides were significantly lower in that group, and the mortality differed only significantly among men below the age of 50. In that group ten died in the placebo group, but none in the treatment group.

The WHO trial. Colestipol was tested in the WHO trial as well. It included ten thousand middle-aged men with hypercholesterolemia, half of which were treated with colestipol. After five years treatment the number of fatal CHD was the same in each group, but the total number of deaths was significantly higher in the treatment group (128 vs 87)²⁵.

The Coronary Primary Prevention trial (CPPT). Despite the general failure of cholesterol lowering strategies to improve cardiovascular outcomes, in 1984 the Coronary Primary Prevention Trial (CPPT) was published in JAMA^{26a}. This trial was praised as the first solid evidence that

reducing cholesterol levels with a pharmacological treatment (cholestyramine) could reduce coronary events and mortality²⁷.

In the CPPT trial^{26b}, middle aged men with cholesterol levels in the top 0.8 % of 480,000 screened subjects were included in the study. Thus, the study was limited to an extreme subset of individuals, which were likely to have had familial hypercholesterolemia. They were treated with either cholestyramine, which lowered their LDL-C levels by about 20%, or a placebo, which produced no significant change. After 7.4 years of treatment, only 30 of 1,906 men in the treatment group (1.6%) and 38 of 1,900 men on placebo (2.0%), had died of CHD; a difference of only 0.4%. In addition, all-cause mortality between the two groups was virtually identical.

These findings should have put an end to the war against cholesterol for two reasons. First, despite the extraordinarily high levels of cholesterol these men were quite healthy; the incidence of coronary events and mortality in this group with hypercholesterolemia was unexpectedly very low. This finding alone is strong evidence against the cholesterol hypothesis. Second, pharmacological reduction of their cholesterol had little effect on outcomes.

One would think that with such strong evidence against cholesterol as a causal agent in heart disease that the directors would have given up their fight to demonize cholesterol. It is surprising that despite the meager findings in the CPPT trial, it was promoted as a pivotal victory. A Time Magazine article stated for example that *Cholesterol is proved deadly ... Lowering cholesterol levels markedly reduces the incidence of fatal heart attacks*. Although the trial was a drug study, the article quoted Basil Rifkind, director of the study, who stated that *the research strongly indicates that the more you lower cholesterol and fat in your diet, the more you reduce your risk of heart disease*.

A consensus conference. Undeterred by the unimpressive findings, the study directors held a consensus conference on cholesterol at the National Institutes of Health²⁸. The aim of this conference was to discuss how the results of the CPPT trial should be translated into dietary guidelines for the American people. The conference was headed by Basil Rifkind, who also chose the members of the panel that formulated the final recommendations.

According to the medical investigative reporter Thomas Moore, who participated in the conference²⁹, there was actually no consensus in the audience. Criticism from the audience was swept under the rug, and some of the critics were cut off by the panel chairman Daniel Steinberg, who cited a lack of time; requests to write a minority report were denied as inconsistent with the conference's goal of a consensus.

As also documented in a recent meta-analysis of the trials performed before the consensus conference³⁰, the dietary guidelines, according to which foods rich in SFA and cholesterol should be exchanged with food rich in carbohydrates and PUFA, were introduced without any scientific evidence. In spite of that, most other countries soon accepted the flawed dietary guidelines as well. Today there is much evidence that a high intake of carbohydrates and omega-6 PUFAs have many adverse effects on health. In accordance both obesity and type 2 diabetes have increased almost epidemically in many countries after the introduction of the American guidelines.

Ignore the contradictions!

The Miettinen trial. In Finland the results from a multifactorial trial was published one year after the publication of the CPPT trial³¹. It included about 1200 middle-aged, more or less overweight male business executives with high cholesterol and high blood pressure. Half of them were given the same advice as in MRFIT. If their cholesterol was high they were even treated with various cholesterol-lowering drugs, whereas the control group continued as before. Again the risk factors changed satisfactorily, but in spite of that twice as many died in the treatment group as in the control group.

You may probably ask how the medical world reacted to this study. Let us therefore see how often their report became cited by other researchers in subsequent years, and let us compare it with how often the CPPT trial was cited. Both papers dealt with the same subject and were published in the same journal, and no one has questioned the honesty of the experimenters or the quality of the studies; at least not the Finnish one. Reasonably, they should have been cited almost equally often. That the CPPT trial, at least according to its directors, was supportive, and the Miettinen trial was not, is

unimportant because the aim of research is to find the truth, whether it supports the current theories or not.

According to Science Citation Index the CPPT trial was cited 109, 121, 202 and 180 times, respectively during the following four years, whereas the Miettinen trial was cited only six, five, three and one time during these four years.

The 2009 WHO/FAO report. In a report from WHO published in cooperation with FAO, 28 experts had been selected to scrutinize the scientific literature about dietary fat³². This time the authors had looked at every type of study. In the section of the study on saturated fat Skeaff and Miller declared that *the available evidence from cohort and randomised controlled trials is unsatisfactory and unreliable to make judgements about and substantiate the effects of dietary fat on the risk of developing CHD*.

But in another section Elmadfa and Kornsteiner declared, that *there is convincing evidence that substituting SFA with mainly PUFAs reduces the risk of CHD*, and in the conclusion of the report, no changes were made as regards the dietary recommendations.

It would appear that the twenty-eight authors didn't confer with each other because Skeaff and Miller's figure 12 clearly shows that a high intake of PUFAs is associated with an increased risk of dying from heart disease, whereas figure 8 shows no association with intake of SFA.

The Statin Trials

Despite the absence of evidence that cholesterol reduction, with either diet or drugs, has been effective in improving health outcomes, the last 20-year epoch has been a clear victory for the advocates. We are now in a period in which the dominant approach to CVD treatment is based on the use of statins. The development of these drugs in the 1990's has almost silenced debate and objections. The statins have been praised as miracle drugs and the best anti-atherosclerotic insurance³³, as well as the most powerful inventions to prevent cardiovascular events³⁴. The praise for their apparent effectiveness has been near universal, with the latest recommendations by the ACC/AHA that statin treatment would benefit as many as half of all older Americans, as well as children and adolescents with elevated levels of

cholesterol³⁵.

The quandary that the reader is faced with is that statins have generated so much support as the saviour of hearts, and yet skeptics have been vocal in their opposition. We have previously provided a thorough assessment of deception as a tool for statin advocates^{36a,37a}. As an example we have chosen the JUPITER trial to show trial directors' strategy to amplify the miniscule benefits from statin treatment and to minimize the adverse effects. We have also included a section about EXCEL, the first primary-preventive statin trial; a trial which should have stopped all future trials on healthy individuals because already after 48 weeks the number of deaths was almost twice as high in the treatment groups as in the control group.

The JUPITER trial. In this trial, rosuvastatin (Crestor) or placebo was administered to 17,802 healthy people with elevated C-reactive protein and normal cholesterol. The primary outcome was a major cardiovascular event³⁸. The trial was stopped after a median follow-up of 1.9 years. The number of subjects with a primary end point was 251 (2.8%) in the control group and 142 (1.6%) in the rosuvastatin group, thus resulting in an absolute risk reduction (ARR) of 1.2 percentage points. The benefit as regards the number of fatal and non-fatal heart attacks was even smaller; 68 (0.76%) versus 31 (0.35%) events, respectively, eg. an ARR of 0.41 percentage points. Thus, less than one half of one per cent of the treated population benefited from rosuvastatin treatment, and 244 people needed to be treated to prevent a single fatal or non-fatal heart attack. Despite this meagre effect, in the media the benefit was stated as “*more than fifty per cent avoided a fatal heart attack*”, because 0.41 is 54% of 0.76.

It is also worth noting that the ARR of 0.41 percentage points was the combination of fatal and nonfatal heart attacks. There was little attention paid to the fact that more people had died from a heart attack in the treatment group. Even experienced researchers may have overlooked this finding because the figures were not explicitly stated in the report. One needs to subtract the number of non-fatal CHD from the number of any myocardial infarction to see that there were 11 fatal heart attacks in the treatment group, but only 6 in the control group.

According to a table in the JUPITER report there was no difference between the numbers of serious adverse effects between the two groups.

However, in the rosuvastatin group there were 270 new cases of diabetes, but only 216 in the control group (3% vs. 2.4%; $p < 0.01$). Unlike beneficial effects, which the authors amplified by using the relative risk reduction (RRR), the significant effect of new onset diabetes was expressed correctly in the ARR form.

An objective assessment of the JUPITER findings should therefore be conveyed to potential patients in the following manner: *Your chance to avoid a non-fatal heart attack during the next two years is about 97 % without treatment, but you can increase it to about 98% by taking a Crestor every day. However, you will not prolong your life and there is a risk you may develop diabetes, not to mention other serious adverse effects.*

But in the media the JUPITER findings were presented as very impressive. In an article in Forbes Magazine, John Kastelein, a co-author of the study, proclaimed: *It's spectacular ... We finally have strong data" that a statin prevents a first heart attack.* Shortly afterwards an FDA advisory panel recommended Crestor treatment for people with elevated C-reactive protein levels and normal levels of cholesterol. As a result Crestor became the second most highly prescribed statin in 2015.

A pertinent question is, why did they stop the trial already after 19 months? According to figure 1 in the trial report the mortality curves of the two groups clearly were approaching each other. Had they continued a few months more, they may have crossed each other, meaning that mortality may have become greater in the treatment group. The significant increase of the number of diabetics might also have increased even more if the trial has continued. A relevant reason to stop a trial is of course, if the outcome becomes worse in the treatment group. Better to stop it before such bad things happen. In the EXCEL trial, the first primary-preventive statin trial, the same strategy was followed.

The EXCEL trial was started by Merck two years after the start of 4S, their second-preventive statin trial. It included 8245 healthy people with high cholesterol divided into five groups, four of which received various doses of lovastatin³⁹. The trial was ended after 48 weeks. According to a correspondence between Merck and UR the reason was that the aim of the trial was to see if lovastatin would lower cholesterol and to see if the participants tolerated the drug; according to the authors, this was indeed the

case.

To plan, develop and initiate a trial including more than 8000 participants from 362 clinical sites takes place at phenomenal cost. Once initiated, the cost of a trial is relatively low and potential benefits of reporting positive effects of treatment come at a minimal cost. It was therefore paradoxical that Merck terminated the trial after only 48 weeks. One wonders, therefore, why they didn't continue the trial? Clearly the costs of continuing that trial would have been minimal compared with the costs starting a new trial. We will provide a logical explanation for its early termination.

With EXCEL, in contrast to almost all other reports from the statin trials, no precise information was provided regarding the number of participants or events in each group. In the placebo group 0.2 per cent died; in the four lovastatin groups the numbers were 0.5, 0.3, 0.6 and 0.5 per cent, respectively. Thus, even if the numbers were small, total mortality was 1.5-4 times higher in the treatment groups after 48 weeks. According to the authors the differences were not statistically significant, but it is easy to calculate, that the difference is close to a p-value of 0.05. Nothing was mentioned about these figures in the abstract.

Stopping the EXCEL trial after 48 weeks had the consequence that it would not be included in any meta-analysis of statin trial outcomes, because all meta-analyses have excluded trials with a duration shorter than one year.

How trial directors have minimized the appearance of adverse effects of statins.

As we have reviewed here and elsewhere^{36b,37b}, the magnitude of the benefits of statin treatment is meager, typically in the range of a one to two percentage point reduction in the rate of coronary events and even lower as regards mortality. Nevertheless, at a global level, a reduction of coronary events and death in 2% of the population could make a substantial difference if the statins were harmless. However, the adverse effects of statins are substantial, including cancer, cataracts, diabetes, cognitive impairment, impotency, renal failure and musculoskeletal disorders. Whereas the benefits are routinely reported as relative risk, adverse effects are always expressed in terms of absolute risk or not at all. In the following we have briefly summarized the deceptive strategies used by the trial

authors to minimize the appearance of adverse effects. More detailed information is available in our published paper^{36c}.

Cancer. Several statin trials have reported an increase in the incidence of cancer in the treated populations. In three of them the increase was statistically significant. In the CARE trial⁴⁰, breast cancer had occurred in 12 (4.2%) of the women in the pravastatin group but in only one (0.34%) in the placebo group. The authors dismissed the significant difference ($p=0.002$) by stating, that *there is no known potential biologic basis...the totality of evidence suggests that these findings in the CARE trial could be an anomaly*. In the two secondary-preventive trials named PROSPER⁴¹ and SEAS⁴², cancer occurred significantly more often as well. The authors of PROSPER downplayed the finding by referring to a meta-analysis of all other pravastatin-trials, which didn't find an excess of cancer, but they did not mention, that on average the participants in PROSPER were 25 years older than those in the other trials. The authors of SEAS classified it as chance, and nothing was mentioned about it in the abstract.

Although the directors of the statin trials typically dismiss a link between statins (or low cholesterol, in general) and cancer, there are well-established mechanisms that can explain a statin-cancer association. For example, it is well established that the lipoproteins participate in the immune system by binding to and inactivating all kinds of microorganisms and their toxic products⁴³, and there is a well-established role of viruses in cancer development⁴⁴. Several case-control studies of cancer patients and healthy controls have also shown that the cancer patients had been using statins significantly more often⁴⁵. Supporters of statin-treatment typically dismiss these findings by referring to meta-analyses of the statin-trials, which report no evidence of an association of statin treatment to the incidence of cancer. There are serious biases in these meta-analyses, however.

First, almost all statin trials ignore reports of skin cancer. This strategy appears to have begun with the two first simvastatin-trials 4S and HPS^{46,47}, in which more patients in the treatment groups were diagnosed with non-melanoma skin cancer. Although these figures appeared in the tables, the authors did not mention this finding in the text, possibly because the differences were not statistically significant, but if the data from both trials

are combined, the statin-skin cancer association was significant (256/12 454 vs. 208/12 459; $p < 0.028$). It is notable that skin cancer is relatively easy to detect at an early stage of development, and its exclusion from the statin reports has introduced a serious underestimation of the number of cancer.

Second, most statin trials are terminated within 2-5 years. As the latent period between exposure to a carcinogen and the incidence and detection of cancer in humans may be 10 to 20 years or more, the absence of any controlled trials of this duration means that we do not know whether statin treatment will lead to an increased rate of cancer in the coming decades. Concern over the risk of statins as carcinogens is validated by experiments, which have shown that serum concentrations similar to those achieved in human beings can produce cancer in rodents⁴⁸.

No significant increase of cancer was seen in a ten-year follow-up of the participants in the 4S trial and the authors therefore concluded that ten years of statin treatment does not induce cancer. Neither does ten years smoking. But in a case-control study of several thousand women there was a doubling of the risk of ductal and lobular breast cancer among those who had used statins for more than 10 years (odds ratio 2.00; 1.26-3.17)⁴⁹.

Myopathy. According to the reports from the statin trials muscular problems occur in less than one per cent of the patients. However, myopathy has only been recorded, if the level of creatine kinase was at least ten times higher than the upper normal level at two successive determinations,

One may wonder if the extraordinarily high threshold for categorizing adverse effects of statins for myopathy is designed to minimize the detection of harm, a strategy which will produce the appearance that statins are harmless, but is inconsistent with the Hippocratic oath whereby the clinician must *first, do no harm*. The fact is that microscopic examinations of muscle tissue from statin-treated patients with muscular symptoms and normal creatine kinase have shown signs of damage⁵⁰. Even patients without overt muscular symptoms may be damaged. In a study of muscle tissue using electron microscopy, the structural integrity of skeletal muscle fibres was compromised in 10 of 14 statin-treated patients without any subjective complaints, compared to one of eight control individuals⁵¹.

According to independent researchers, myopathy is the commonest

adverse effect of statins, and is seen more often in women and elderly people. For instance, Sinzinger et al. have reported that muscular weakness and pain occur in one out of four statin-treated patients who exercise regularly⁵². They also noted that seventeen out of twenty-two professional athletes with familial hypercholesterolemia treated with statins stopped because of that particular side effect⁵³. Furthermore, in an RCT that included 1016 healthy men and women with high LDL-C, Golomb et al found that after six months statin treatment 40% of the women suffered from exertional fatigue⁵⁴.

Another way to minimize the muscular symptoms is to separate them into numerous categories. According to the FDA Adverse Event Reporting System (FAERS), adverse muscular symptoms are recorded in 11 categories (muscle disorder, myopathy, muscle tightness, musculoskeletal stiffness, myalgia, muscular weakness, muscle cramp, muscle enzyme, muscle fatigue, muscle necrosis and muscle spasm). In most of them a low incidence are reported, but taken together the number of myopathy-related events is substantial.

Muscular side effects are not benign phenomena; they may in particular have a deleterious effect on elderly people, because the least expensive and the least risky way to prevent heart disease is regular exercise. Even worse is that severe muscular damage may cause serious renal diseases. In a 6.4 year long follow-up study including 6342 statin-treated "patients" and 6342 non-treated controls corrected for many variables, almost 4 % more in the statin group suffered from acute renal failure, chronic kidney disease, nephritis, nephrosis or renal sclerosis⁵⁵.

Neurological effects. Nothing is mentioned about cerebral side effects in the statin trials, although several independent researchers have reported that such symptoms are common. For example, in a meta-analysis of cholesterol lowering trials, Muldoon et al found a statistically significant increase in the number of deaths from accidents, suicide, or violence in the treatment groups⁵⁶. Furthermore, it has been shown by several authors that low cholesterol is a biological marker of major depression and suicidal behavior, whereas high cholesterol is protective^{57,58}. In accordance Davison et al. found that the incidence of suicidal ideation among adults with mood

disorders was more than 2.5 times greater in those taking statins ⁵⁹. Moreover, several studies have shown that low cholesterol is associated with poorer cognition and Alzheimer's disease, and that high cholesterol is protective⁶⁰. For instance, in a study of 143 patients with memory loss or other cognitive problems associated with statin therapy, Evans and Golomb reported that 90% of them improved after discontinuation of their statin treatment⁶¹. In a study by Padala et al. eighteen older statin-treated subjects with Alzheimer's disease were asked to stop their statin treatment. Twelve weeks later, their performance on several cognition tests had improved significantly and after having started the treatment again, their performance on the tests worsened significantly⁶².

There are at least two reasons why such symptoms are ignored in the statin trials. The cerebral symptoms usually do not occur immediately. If they occur in elderly patients several weeks or months after the start of the treatment, both the doctor and the patient may interpret them as symptoms of advancing age. The other reason is that cerebral side effects are classified into many different subgroups. According to FAERS, adverse events from cerebrospinal dysfunctions are classified in 23 separate terms (suicidal attempt, suicidal ideation, suicidal behavior, aphasia, balance disorders, coordination abnormal, amyotrophic lateral sclerosis, amnesia, memory impairment, transient global amnesia, cognitive or confusional state, irritability, paranoia, disorientation, dementia, depression, depressed mood, neuropathy, pain in extremity, Guillain-Barre syndrome, ALS and multiple sclerosis). The incidence of statin-related side effects in the many different subcategories is present at a low rate, but if all of them were to be combined, the total number of adverse events may be substantial.

With the high incidence of neuromuscular adverse effects, it is reasonable to ask why the FDA has not been more forthcoming about informing the public about the well-documented muscle and neurological adverse effects of statins.

About unethical reporting. *Adverse effects from statin treatment are very rare.* This is what Sir Rory Collins, Professor of Medicine and Epidemiology at Oxford told the media in a fierce comment to two papers published in British Medical Journal (BMJ) where the authors claimed that 18%-20% of patients on the cholesterol-lowering drugs suffered adverse

events. According to Collins side effects occur in only one in 10,000 people, and he therefore insisted that BMJ should withdraw the papers, but Collins' protest only resulted in a correction of a minor error.

The large difference between the number of side effects according to the trial reports and those reported by independent researchers has led several researcher to ask the trial directors for access to the primary data, but this has always been denied. By this reason new penal EU regulations on clinical trials came into effect in 2004 according to which *essential documents must be archived and be accessible for audit and inspection by regulatory authorities*⁶³. It is a striking fact that the benefits recorded in statin trials published since then have become minimal or totally absent⁶⁴.

How to cover up that high cholesterol is not a risk factor. Almost everyone “knows” that high cholesterol is a risk factor for heart disease, but as mentioned above, many studies have shown this apparent truism is actually incorrect. The idea was promoted by the Framingham group after their first follow-up of a group of middle-aged inhabitants in the town. However, in the 30-year follow-up of these people they found, that high cholesterol was not a risk factor after the age of 47. In fact, high cholesterol seemed to be beneficial, because, as they wrote: *For each 1 mg/dl drop of cholesterol there was an 11% **increase** in coronary and total mortality*⁶⁵.

With these results in hand why did the authorities not reveal to the public the great value in maintaining high levels of cholesterol with advanced age? Because the findings were ignored, or more directly, the directors misrepresented them entirely, i.e., they lied about the findings. In an extraordinary feat of deception, reminiscent of “doublethink”, the highly refined form of deception in George Orwell's novel, *Nineteen Eighty Four*, the 30-year follow-up of the Framingham project is instead used as *support* of the cholesterol hypothesis. Consider for instance the joint statement by the American Heart Association and the National Heart, Lung and Blood Institute in their review entitled *The Cholesterol Facts: The results of the Framingham study indicate that a 1% reduction.....of cholesterol corresponds to a 2% reduction in CHD risk*⁶⁶, and here they refer to the opposite result of the 30-year Framingham follow-up study.

One of their strongest arguments is an analysis of the screenees in the WHO trial. The figures from this trial included both the 12,000

participating men, but also the more than 300,000 men who were excluded for various reasons. A large number of studies concerning the follow-up of these people has been published in well-known international medical journals, and these studies are cited again and again as the strongest proof that there is a linear association between blood cholesterol concentrations and the risk of future heart disease.

But these data are not reliable. In a systematic search of the literature on the MRFIT study, Lars Werkö, then director of the Swedish Council on Technology Assessment in Health Care, an independent governmental agency known for its integrity, found 34 papers based on data from MRFIT reporting the relationship between serum cholesterol and mortality⁶⁷. He asked himself whether it really was necessary to publish all these reports, as their results were so similar. *Have the editors really judged the original scientific value of each of these similar articles and deemed them worthy of publication? Or have they been impressed by the status of the research groups that authored these repetitive manuscripts, with the prestigious National Heart, Lung and Blood Institute in the background, and found that they have to succumb to the authorities?*

Worse than being repetitive, the data were inconsistent and of questionable veracity. For instance, the number of screenees varied greatly between the studies, from 316,099 to 361,266. In particular, Werkö was critical of the studies reporting how many had died and why, because it is highly unlikely that all of 361,266 individuals could have been tracked after 6-12 years.

How the cause of death had been established was not reported but we can be rather confident that most of the reported causes were based on death certificates written by general practitioners. Not only is the information from death certificates highly unreliable, but in up to 20% of the reports, death certificates were missing. Yet some of the reports gave a detailed list of diagnoses for almost all deaths.

Furthermore, during the initial screening it came to light that one of the participating centers had falsified its data to increase the number of participants in the trial, possibly in order to obtain more financial support from the National Institutes of Health. This embarrassing matter received little mention in the follow-up reports, nor did the study authors mention the

possibility that data falsification could have occurred in other centers as well. Wrote Werkö: *In the many publications regarding the MRFIT screenees, it is obvious that the authors are more interested in the mathematical treatment of large figures than in the quality of these figures or how they were obtained.*

In spite of all these irregularities, the follow-up reports on the MRFIT screenees are still cited as *the most exact database regarding the relation of risk factors to mortality in the healthy male US population.*

Similar methods have been used by others. In an analysis of the statements by three major American consensus committees it appeared that of twelve groups of controversial papers only two of them were quoted correctly, and only in one of the reviews. About half of the papers were ignored. The rest were quoted irrelevantly; or insignificant findings in favour of the hypothesis were inflated; or unsupportive results were quoted as if they were supportive. Furthermore, only one of six randomized cholesterol-lowering trials with a negative outcome were cited and only in one of the reviews, whereas each review cited two, four, and six non-randomized trials with a positive outcome, respectively⁶⁸.

Conclusion

The war on cholesterol is reminiscent of the Hans Christian Andersen story of the emperor who had been deceived by swindlers who sold him magnificent clothes, which were invisible to all but the feeble-minded. The king, his advisors and the townspeople were all afraid to admit that the clothes were invisible to them. In this chapter we have served in the role of the child, who stated that the emperor wore no clothes. In like manner, we have spoken out against conformity to the prevailing, but incorrect, view of cholesterol as inherently atherogenic. We have scrutinized the literature to describe how dominant figures in the field of heart disease have, for decades, created the illusion that cholesterol causes heart disease and that the diet and drug-induced reduction of cholesterol is beneficial to cardiovascular outcomes. We have described how advocates of the war on cholesterol have created the illusion that cholesterol is atherogenic by ignoring all conflicting observations from critical and independent scientists, by citing studies incorrectly to make them look supportive of the

cholesterol hypothesis, and with the use of deceptive statistics which have distorted and exaggerated trivial findings.

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Chapter Eight

People with High Cholesterol Live Longer

Tomohito Hamazaki, MD, PhD

Abstract

High blood cholesterol is recognized as a major cause of coronary heart disease (CHD). Although cholesterol levels in Japan are just the average of Western European countries, its CHD mortality is very low compared with those countries. In fact, all-cause mortality in Japan is inversely correlated with LDL-cholesterol levels irrespective of age and sex. The only exception in Japan to this finding is NIPPON DATA80 study (ND80), in which the all-cause mortality of the highest cholesterol group (both sexes combined) was significantly higher than that of the other groups. This phenomenon can be reasonably explained by higher proportions of familial hypercholesterolemia in the ND80 cohort than in the other study cohorts. (Cholesterol is not the cause of CHD in familial hypercholesterolemia though; see the text.) The Cholesterol Guidelines of Japan Atherosclerosis Society (2012) used ND80 results for the most important chart of the Guidelines, which indicated the relationship between 10-year CHD mortality, and sex, age, smoking, blood pressure and cholesterol. However, the unfortunate point is that the number of CHD deaths included in the men's chart was only 18 deaths or so in 10 years; furthermore no mention of statistical significance was made. MEGA Study, the top intervention study with statin in Japan, had serious flaws, and was hardly able to prove any beneficial effects of statin. Cholesterol is a friend; it should not to be feared as dangerous. Neither epidemiological nor intervention studies have been able to prove that cholesterol is the enemy in Japan—the country where there has been low CHD mortality from the outset and where anti-cholesterol myth campaigns can be conducted more easily than in any other countries.

Introduction

In Japan, the four leading causes of death are cancer, heart disease, pneumonia, and stroke, in that order ^{1a}. Mortality from ischemic heart disease (IHD) ^{*} accounts for about 40% of heart disease, but only 6% of all-cause mortality ^{1b}. If mortality from a certain disease (IHD for instance) could be reduced by two-thirds in any country, it would be an astonishing success. In fact, Japan has succeeded in doing this from the very outset in a sense. As we can see in Fig 1, Japan is lucky enough to enjoy the lowest age-specific mortality from IHD among some 14 countries ^{2a}, at roughly one-third of the mean mortality of the other countries. Why is IHD mortality so low in Japan? The major reason is probably that Japanese people regularly eat a lot of fish and have a high intake of α -linolenic acid. So, do they have very low cholesterol levels? Actually they don't. If we look at the cholesterol values of the countries listed on the right in Fig 1, which are the mean values for 2005 through 2009 for both sexes ^{3a}, the median cholesterol value of those countries (5.2 mmol/L or 200 mg/dL) is randomly scattered among them. This does not support the notion that cholesterol is an important risk factor for IHD.

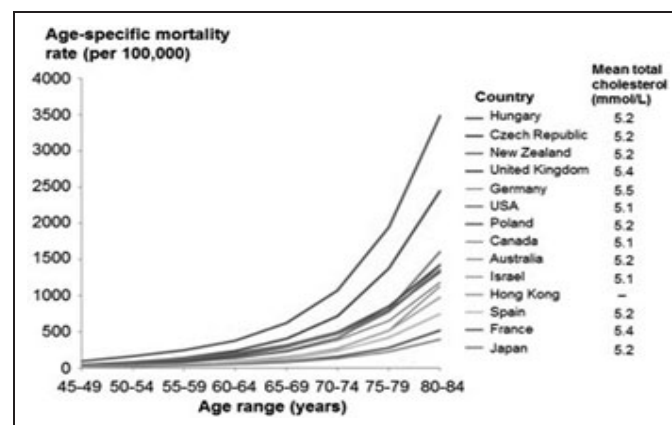


FIGURE 1 Age-specific mortality rate of ischemic heart disease for 14 countries

The most recent year of available data between 2005 and 2009 is shown ^{2b}. The mean total cholesterol values between 2005 and 2009 were calculated from the table provided by WHO ^{3b}.

Moreover, Sekikawa et al ⁴ reported very interesting trends in blood cholesterol levels and mortality from coronary heart disease (CHD) in the following 8 countries: Australia, Canada, France, Japan, Spain, Sweden, the

UK, and USA. Age-adjusted CHD mortality continuously declined between 1980 and 2007 in all these countries. The decline was accompanied by a constant fall in total cholesterol except for in Japan where total cholesterol levels continuously rose. With Fig 1 in mind, is this a Japanese paradox so to speak? In fact, as explained in this chapter, cholesterol issues in Japan are much more than that. Cholesterol levels are a good indicator of longevity irrespective of age and sex. If you look at cholesterol issues in Japan, you will clearly understand what cholesterol is—a friend, not an enemy.

What's important is how many people with familial hypercholesterolemia are in the cohort

Before explaining the issue of cholesterol in Japan, I would like to point out the key to understanding the situation between cholesterol and CHD, namely, the existence of familial hypercholesterolemia (FH). Although many epidemiological studies point to hypercholesterolemia as the cause of CHD, most importantly, mean cholesterol levels do not differ between individuals with heterozygous FH who develop it and those who do not (see Fig 3-A in a previous review^{5a} for details). Because cholesterol levels and CHD mortality are both much higher in individuals with homozygous FH than in those with heterozygous FH, the similar cholesterol levels seen between individuals with heterozygous FH with CHD and those without CHD cannot be explained by the ceiling effect of cholesterol. Instead, abnormalities of the hemostatic system in FH may explain the high CHD incidence⁶. It is also possible that the LDL receptor defect in FH causes undernutrition of the arteries; through the LDL receptors, LDL particles provide the important nutrients of lipid soluble antioxidants and triglycerides to blood vessels as well as provide the cholesterol necessary for blood vessel repair. At any rate, the association between high cholesterol levels and CHD mortality in Japanese men is most likely due to the presence of individuals with FH in the very high cholesterol groups examined. As for Japanese women, CHD mortality has rarely shown an association with cholesterol levels (the panel for women in Fig 3 is a good example); in the Jichi Medical School Cohort Study, no deaths from myocardial infarction were found at the highest total cholesterol levels (≥ 6.21 mmol/L or ≥ 240 mg/dL) in about 7,500 women aged 40-69 years

during an average follow-up of 11.9 years⁷—another “Japanese paradox”, if you will.

For the association of CHD mortality with cholesterol to be explained by the presence of FH, the slope of the association between cholesterol and CHD mortality would become flatter and flatter as the cohort ages, and there would be fewer and fewer CHD-prone FH participants in the cohort. In fact, this is precisely the case in many epidemiological studies, as Okuyama et al first reported⁸ (see also Chapter 3 of our review^{5b}).

Cholesterol levels and all-cause mortality in Japanese people

Do Japanese people really live longer with higher cholesterol levels irrespective of age and sex? If they do, this must provide the answer to many so-called cholesterol paradoxes and inform us about how to deal with cholesterol.

Let us take a quick look at the largest Japanese epidemiological study on cholesterol undertaken to date. Men and women (N=91,219) aged 40-79 years with no history of stroke or CHD were followed for 10.3 years in the Ibaraki Prefectural Health Study^{9a}. Figure 2 shows the relationship between all-cause mortality and LDL cholesterol. The hazard ratio (HR) for all-cause mortality was calculated according to LDL cholesterol levels with adjustment for age and many potential confounding factors, and revealed that all-cause mortality was essentially inversely correlated with LDL cholesterol levels in both men and women. The first reaction of well-informed advocates of the cholesterol theory to the findings of this Japanese study would be that this kind of phenomenon can be easily explained by the presence of participants with an as yet subclinical serious disease (e.g., hidden cancer), where some of them who had lower cholesterol levels due to their hidden disease died during the study period (reverse causality). To exclude this possibility of reverse causality, the authors of the Ibaraki Prefectural Health Study re-analyzed the data excluding deaths that occurred within the first 2 years after baseline measurement and, interestingly, found that their initial results were not substantially changed^{9b}.

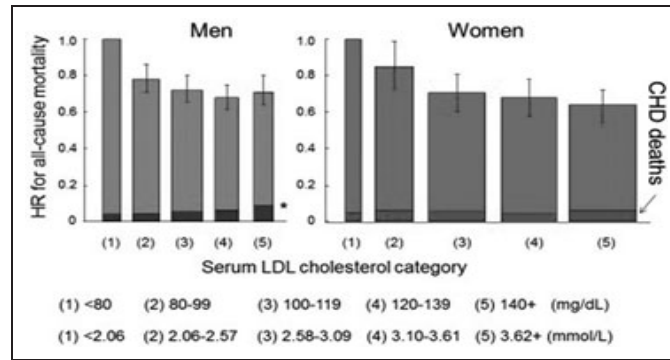


FIGURE 2 Relationship between serum low density lipoprotein (LDL) cholesterol level and the hazard ratio (HR) for all-cause mortality: Ibaraki Prefectural Health Study^{9c}

*A total of 30,802 men and 60,417 women were followed for a median 10.3 years. HRs were adjusted for age and many potential confounding factors. Darker colors represent CHD deaths. The height of the bar for CHD deaths is set according to the ratio between the number of CHD deaths and the number of all-cause deaths in the respective groups. The width of each column is proportional to the number of participants in that group. The vertical lines represent 95% confidence intervals. HRs for all-cause mortality for each standard deviation increment of LDL cholesterol were 0.88 (0.85-0.91) for men and 0.90 (0.86-0.93) for women. (Created from the data given in Tables 1 and 2 of reference 9.) *: Significantly different from the reference group (<80 mg/dL) with regard to CHD deaths.*

Figure 2 also shows the relationship between LDL cholesterol levels and CHD mortality (indicated by darker colors) according to sex. In men, the HR for CHD mortality was significantly higher than that of the lowest group. However, in women, no differences were observed between any groups. Figure 2 is a good representation of the situation in Japan with regard to cholesterol. This relationship between cholesterol and CHD mortality is not linked to genetic differences between Western and Japanese populations. Japanese emigrants to Hawaii, where Japanese culture is still preserved to a certain degree, were shown to have CHD mortality rates intermediate between those of Japanese men living in Japan and those of Japanese American men living in San Francisco, where the latter group had CHD mortality similar to the general population in San Francisco¹⁰.

Similar results were also found in the Isehara Study, which analyzed the data collected from the annual checkups of residents in Isehara City (population: about 100,000) between 1994 and 2004, with a mean follow-up of 7.1 years^{11a}. (Since 1982, Japanese citizens aged ≥ 40 years have been eligible for annual health checkups by law.) The final database for 8,340 men (aged 64 ± 10 years) and 13,591 women (61 ± 12 years) was compiled

after applying the following exclusion criteria: death within 1 year of baseline, incomplete lipid data, attended a single check-up only, and serum triglyceride levels beyond the Friedewald equation limits (4.5 mmol/L or 400 mg/dl; 198 men, 126 women). Mean blood LDL cholesterol levels were calculated for individuals from all their available LDL cholesterol values except that at their last checkup. As shown in Fig 3, LDL cholesterol was again found to be a negative risk factor for all-cause mortality.

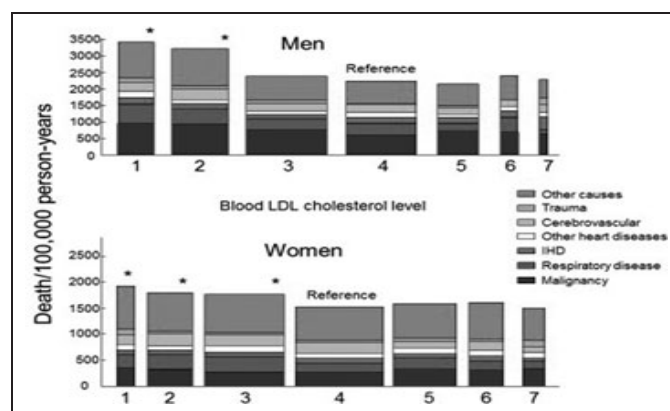


FIGURE 3 Low density lipoprotein (LDL) cholesterol and mortality in the Isehara Study^{11b}

Over 11 years (1994-2004), 8,340 men (aged 64 ± 10 years) and 13,591 women (61 ± 12 years) were followed in Isehara City, Japan. Deaths during the first year of follow-up were excluded. Mean follow-up period was 7.1 years. Cox's proportional hazards regression analysis was employed to calculate age-adjusted relative risks in both men and women. The width of each column is proportional to the number of participants in that group.

Cholesterol level of each category is as follows (mg/dL, mmol/L): category 1: <80, <2.1; category 2: 80-99, 2.1-2.5; category 3: 100-119, 2.6-3.0; category 4: 120-139, 3.1-3.5; category 5: 140-159, 3.6-4.0; category 6: 160-179, 4.1-4.6; category 7: ≥ 180 , ≥ 4.7 . *: $p < 0.001$, Cox's proportional hazard regression analysis with Bonferroni adjustment. (Redrawn with permission from the publisher, with slight modifications.)

A very exceptional study: NIPPON DATA80

There is one very exceptional Japanese epidemiological study in which participants with the highest total cholesterol levels had the highest all-cause mortality. This was the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980, known as NIPPON DATA80 (ND80)^{12a} (see black bars in Fig 4). Figure 4 is a carefully redrawn version of the original figure^{12b} with some important information that I newly added in red. In this study, 9,216

participants were followed for 17.3 years. However, we must exercise extreme caution in interpreting the results. First, let's examine the results of ND80 without combining data from both sexes. Figure 5, which I created from the data given in Table 2 of the same ND80 report^{12c}, shows that neither men nor women had significantly higher all-cause mortality in the higher or highest cholesterol groups at all. In fact, all-cause mortality in the highest cholesterol group was only significantly higher when both sexes were combined, as indicated by the black bars in Fig 4. Moreover, their data were adjusted for serum albumin levels. Because albumin, a good marker for longevity, correlates well with cholesterol level, the adjustment for albumin diminishes the good characteristics of cholesterol. Comparing two figures from the same study (Figs 4 and 5 here), the readers can see how the authors of ND80 exaggerated the risk of high cholesterol levels; they even erased the zero point of the hazard ratio for all-cause mortality. There are more exaggerations: for example, the gray bars are results without deaths due to liver disease (Fig 5), meaning these bars no longer indicate all-cause mortality.

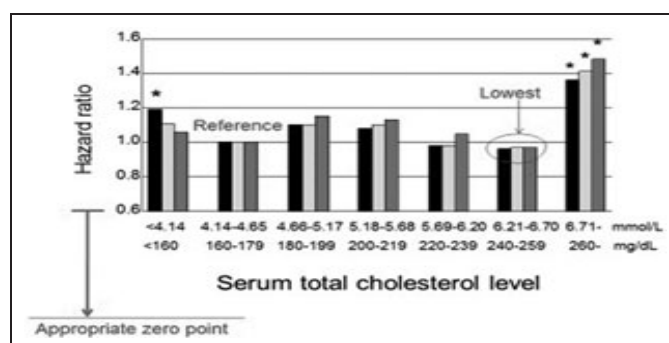


FIGURE 4 Hazard ratio (HR) for all-cause mortality according to serum total cholesterol level: NIPPON DATA80 study, 17.3 years of follow-up^{12d}

*More than 9,000 participants aged ≥ 30 years were followed for 17.3 years. All data sets (black, gray, and hatched bars) were combined data for both sexes. HRs of all-cause mortality were adjusted for sex, age, serum albumin levels, body mass index, hypertension, diabetes, smoking, and drinking. Black bars: HRs for all-cause mortality without any exclusions. Gray (middle) bars: HRs for all-cause mortality after excluding deaths from liver disease during the entire follow-up period. Hatched (right) bars: HRs for all-cause mortality after further excluding all-cause deaths within the first 5 years of follow-up. Whatever technique the authors of the NIPPON DATA80 might have used to emphasize the risk of hypercholesterolemia, participants in the cholesterol range 6.21-6.70 mmol/L (240-259 mg/dL) show the lowest risk of all-cause mortality. *: $p < 0.05$. (Redrawn with permission from the publisher; with slight modifications.)*

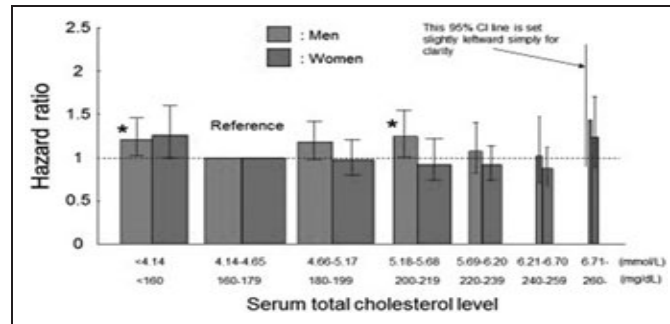


FIGURE 5 Hazard ratio for all-cause mortality by sex according to serum total cholesterol level: the same data from NIPPON DATA80 study^{12c}

Black bars from Fig 4 are presented in a different way. See the legend to Fig 4 for details. HRs are shown here according to sex. The zero line is clearly shown in this figure. Note that if the data were not adjusted for albumin, the HRs for the highest cholesterol groups would be lower and the HRs for the lowest cholesterol groups would be higher. The width of the column of each group is proportional to the number of participants in that group. *: Significantly different from the reference group. (Created from the data given in Table 2 of reference 12.)

So why were the HRs of all-cause mortality slightly high in the highest cholesterol groups of ND80 irrespective of significance in the first place? The answer is very simple: the proportion of participants with FH reported in NIPPON DATA80 is reasonably estimated to be 3-fold higher than that in the general population among male participants and 1.5-fold higher in female participants. (The proportion of FH participants was calculated using the difference between the mean and median cholesterol values in comparison with the general Japanese population^{5c}.) The presence of more FH participants in the ND80 cohort was due to, first, probably a higher proportion of participants with high cholesterol given that the Japanese title of ND80 includes the term “circulatory disease” and, second, the recruitment of ND80 participants from 300 districts across Japan, which made it easy to recruit more FH participants than recruiting them from only one area, especially when the number of participants was large.

Unfortunately, ND80 with its 19-year follow-up¹³ served as the basis for the most important charts given in the 2012 guidelines of the Japan Atherosclerosis Society¹⁴. The charts beautifully show straightforward, positive relationships between 10-year CHD mortality and age, blood pressure (BP), total cholesterol levels, and smoking status, although relationships with age and smoking status only were found in women. Many Japanese physicians follow these 2012 guidelines out of fear of

possible malpractice law suits. However, the most unfortunate point is that the number of CHD deaths included in the men's chart was only 35 or so in 19 years, which is very close to 18 deaths in 10 years. How can a chart be drawn indicating absolute CHD mortality in 10 years according to 6 cholesterol categories, 5 BP categories, 3 age categories, and 2 smoking status categories (180 subgroups as a total)? Moreover, the highest risk of CHD mortality in the group with the highest BP, highest cholesterol levels, highest age group, and who were smokers (5-10% in 10 years) was >10 times higher than that in the youngest (40s) group who were non-smokers (<0.5% in 10 years). While this is mathematically possible, we have to question whether there is any clinical or epidemiological importance here, given that no mention of statistical significance was made.

What happens in elderly Japanese people?

When we look at cohorts of elderly people, the proportion of CHD-prone FH participants is very small and negligible, and only beneficial effects of cholesterol are shown in them. Two epidemiological studies with elderly Japanese people have been reported, both of which show that high cholesterol levels are good for longevity.

The first of these studies, the Tokyo Metropolitan Institute of Gerontology Longitudinal Interdisciplinary Study on Aging (TMIG-LISA) Study followed 1,048 Japanese individuals aged 65-85 years living at home in Tokyo or Akita Prefecture for 8 years^{15a}. As shown in Fig 6, the survival rate was lowest for the lowest quartile of total cholesterol and highest in the highest quartile (without any adjustment). As can be seen from the figure, the relationship between the lowest and highest cholesterol groups does not markedly change with the exclusion of deaths during the first 3 years of the study. The multivariate HR for all-cause mortality for the lowest quartile of total cholesterol was 1.51 compared with the reference (highest quartile) after adjustment for 15 possible confounding factors including grip power and usual walking pace.

The second study of Japanese elderly participants focused on 207 participants only. However, they were all 85 years old at the start, lived in Fukuoka Prefecture, and were followed for 10 years^{16a}. The mortality rates according to serum total cholesterol levels were 77.4%, 62.5%, and 50% in

the bottom, middle, and top tertiles, respectively (Fig 7). A multivariate Cox proportional hazards regression model, with adjustment for sex, smoking, alcohol intake, history of stroke or heart disease, serum albumin concentration, body mass index, and systolic BP, revealed that the total mortality in the bottom tertile was 1.7-fold higher than that in the top tertile. Without albumin adjustment, the difference might have been larger (see above for the discussion on albumin).

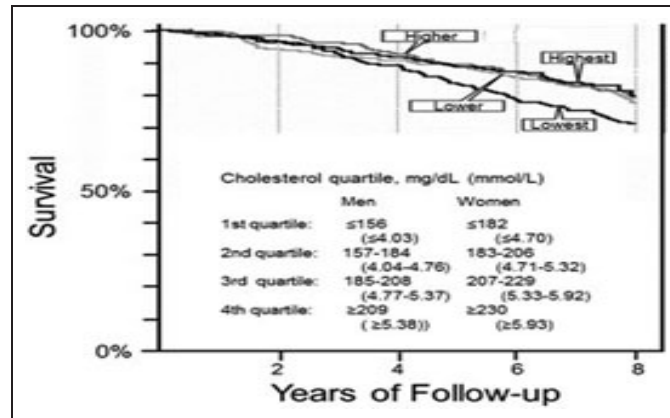


FIGURE 6 Survival curve according to cholesterol quartile in Japanese elderly people: TMIG-LISA Study^{15b}

A total of 1,048 elderly participants were followed for 8 years. Survival rates are depicted according to cholesterol quartile. No adjustment was performed. The hazard ratio for the 1st quartile was 1.51 compared with that of the 4th quartile after adjustment for 15 factors. (Courtesy of Dr Shoji Shinkai, with slight modifications.)

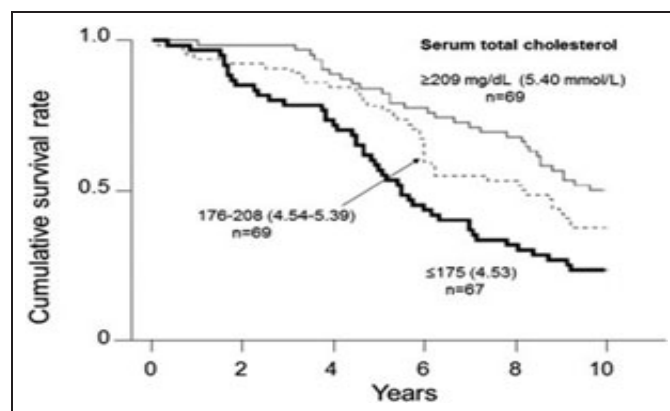


FIGURE 7 Survival curves of very old participants according to tertiles of total cholesterol level: a study in Fukuoka Prefecture^{16b}

Participants all aged 85 in Fukuoka Prefecture were followed for 10 years. Participants in the top and intermediate tertiles of total cholesterol levels survived longer than those in the bottom tertile.

See the text for details.

Are statins effective in Japan?

The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study is essentially the only statin trial in Japan with a seemingly valid control group (only half-valid, though, as discussed below). It was designed as a prospective randomized, open-labeled, blinded-endpoint (PROBE) study^{17a}. Because this study is the most important and influential intervention study in Japan, I will discuss it in detail. Men and postmenopausal women weighing ≥ 40 kg, aged 40-70 years, and with total cholesterol values of 5.69-6.98 mmol/L (220-270 mg/dL) were enrolled between February 1994 and March 1999. Note that this period is of critical importance in understanding the nature of the then diet. Individuals with familial FH or a history of CHD or stroke were excluded. Half of the participants were randomly assigned to the diet alone group and the other half to the diet + pravastatin (10-20 mg/day) group. Follow-up of 5 years was planned.

Unfortunately, this study was seriously flawed. First, randomization seems to have been broken due to a protocol violation: “on the basis of recommendations from the data and safety monitoring committee, the study was continued for an additional 5 years to increase the number of events”^{17b}. This means that the committee considered there were too few events to obtain significant results at the 5-year mark; so again, Japanese people succeeded in having low CHD mortality from the beginning.

Second is a point that even lay people might have some doubts about (see Fig 9). No CHD cases were observed for more than 1 year starting just before the end of originally planned intervention of 5 years. This looks extremely unnatural. Healthy participants must have been selected in the diet + pravastatin group, intentionally or unintentionally. Actually the numbers of participants in both groups dropped suddenly after 5 years. This study should have reported only the results obtained at the end of the first 5 years.

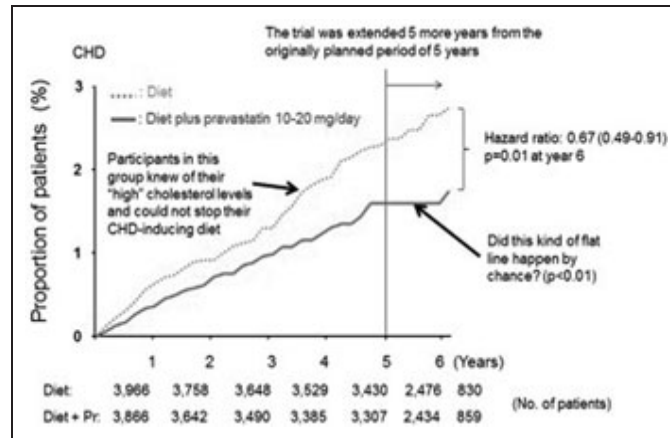


FIGURE 8 Kaplan-Meier curves for the primary endpoint of first occurrence of coronary heart disease: MEGA Study^{17c}

Patients with hypercholesterolemia without any history of CHD or stroke were randomly assigned to the diet or diet + pravastatin group for the mean follow-up period of 5.2 years^{17d}. CHD was significantly lower in the diet + pravastatin group than in the diet alone group (66 versus 101 events, $p=0.01$). Besides the flaws described in the text, there are more: the ratio of participants who could not be confirmed to be alive was significantly higher in the pravastatin + diet group than in the diet alone group. Hama et al¹⁸ collected relevant data from papers published on the MEGA Study and from the study's website and also obtained a Japanese version of a slide set on the MEGA Study presented at the American Heart Association Scientific Sessions, 2005. According to the Japanese slides, 13.5% of participants in the pravastatin + diet group compared to 11.9% of participants in the diet alone group could not be confirmed to be alive (odds ratio: 1.16, 1.01-1.33, $p=0.031$). Also, participants who were diagnosed with cancer within the first 6 months of the study were excluded from the analysis. (Remade with permission from the publisher, with slight modifications.).

Let's look at the results for the first 5 years only. The incidence curve of the diet group is above that of the diet + pravastatin group irrespective of significance. Why is this so? The authors of the study would say with confidence that it was because of statin, but my answer is completely different; it was because of diet. Probably the readers of this chapter have no real experience of the unfortunate reason for this: according to the thinking of that time, the diet recommended for the MEGA Study participants was not nutritionally appropriate for CHD prevention. Butter was replaced with margarine rich in linoleic acid and/or *trans* fatty acids, and fatty fish was avoided because of its high cholesterol content. In fact, as we know now, this diet was CHD *inducing*. The diet + statin group did not likely stick to the diet because they and their doctors knew that their cholesterol levels decreased soon after statin prescription, and thus they

thought that the diet were no longer necessary. However, the “diet alone” participants could do nothing except stick to the harmful diet (because it was the only major intervention recommended to them to reduce their risk for CHD) and therefore they had higher incidental CHD than the diet + statin group. This appears to be the major reason for the difference in IHD incidence between the two groups.

Another very important problem with this study was that it was open-label and participating physicians were presumably pro-statin, otherwise they wouldn't have participated in the study. Therefore, the differences in angina and revascularization events between the two participant groups should be discounted. Both of these events were dependent on the physicians' subjective judgment, especially if they viewed those patients who were not receiving the statin to be at higher risk for CHD than those receiving it. If we discount these two events that are open to subjective bias, there would be no difference between the two groups irrespective of significance.

There are some other problems with the study, which are mentioned in the legend to Fig 8. So, even the most important statin-intervention study did not actually prove anything much at all about CHD prevention in Japan.

Conclusions

Cholesterol is in fact a friend; it should not to be feared as dangerous and we should not try to reduce our blood levels of it. Neither epidemiological nor intervention studies have been able to prove that cholesterol is the enemy. This situation is especially clear in Japan—*the* country where there has been low CHD mortality from the outset and where anti-cholesterol myth campaigns can be conducted more easily than in any other countries.

What an irony it is that the first statin was discovered in Japan!

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Chapter Nine

A Role for Sulfur Deficiency in Coronary Heart Disease

Stephanie Seneff, PhD

Abstract

Despite decades of research, many questions remain unanswered about the pathogenesis of cardiovascular disease. Why does cardiovascular plaque accumulate only in arteries, and preferentially in arteries supplying the heart? Multiple pathogenic microbial species take up residence in the plaque, yet antibiotic therapy has generally been unsuccessful. Inflammation is now believed to be a critical factor, yet the question of why inflammation occurs itself remains unanswered. Geographical studies show a strong inverse relationship between sunlight availability and heart disease, yet studies on vitamin D supplements have been disappointing. Here, I propose a unifying theory for the etiology of cardiovascular disease, where the atheroma develops to supply cholesterol sulfate to the heart, due to pathologies in the normal supply chain. Sun avoidance and consumption of chemical-laden processed foods are major contributors to the development of coronary atherosclerosis. Appropriate preventive measures include sulfur-containing foods and supplements, organic diet, and sun exposure.

Introduction

Despite many decades of research, atherosclerosis remains a poorly explained phenomenon. The field of cardiovascular disease is in a state of confusion, as doctors continue to focus on high serum cholesterol levels as the main culprit, whereas correlations between cholesterol and ischemia risk are low and insignificant. On the other hand, while factors such as various infective agents and elevated serum homocysteine are correlated with heart disease risk, active treatment of these conditions consistently

fails to show benefit. The simple story that is presented to the public is that excess cholesterol accumulates in the blood and lodges in the artery wall, eventually obstructing flow. However, it is striking that the lipid deposits accumulate only in arteries – never in veins. And what is even more striking is that the arteries supplying the heart are the most vulnerable.

In this chapter, all of these seemingly contradictory facts are explained via the theory that heart disease is a condition resulting from deficiencies in the supply of cholesterol sulfate to the vasculature. The atheroma is then viewed as a site where cholesterol sulfate is actively synthesized, and the sulfate is later redistributed to the capillary wall to protect from vascular damage and support the smooth passage of red blood cells. The atheroma is constantly remodelled as its components are repeatedly built up and broken down by metalloproteinases. The deficiency comes about because the enzymes that normally maintain serum levels of cholesterol sulfate are disrupted by environmental toxicants, such as aluminum and glyphosate.

According to this alternative view, the atheroma subserves the heart by providing it with vital nutrients, namely, cholesterol and sulfate. It follows that the cause of heart disease is inadequate supply of cholesterol sulfate to the heart. I will further argue that cholesterol sulfate is normally produced in the skin by keratinocytes, red blood cells, and platelets, catalyzed by sunlight. This theory predicts that sunny climates reduce heart disease risk and that sulfur-rich soil and water derived from basalt rock are protective. Indeed, France and Spain have much lower rates of death from myocardial infarction (MI) than the United Kingdom, and people living on islands enriched with sulfur-containing volcanic basalt rock, such as Japan, Iceland, and Crete, enjoy low MI risk and extended life expectancy.

Early studies on primates showed that a high-fat, high-cholesterol diet fed to monkeys could induce atherosclerosis, but that simultaneous supplementation with sulfur-containing metabolites was protective¹. Similarly, experiments on rats showed that a diet supplemented with excess cholesterol, cholic acid and vitamin D2 can induce aortic lesions expressing calcification and plaque formation, but such lesions can be completely prevented by simultaneous supplementation with chondroitin sulfate². Children with disorders of cysteine metabolism develop arterial damage at an early age resembling atherosclerosis³. The consumption of garlic is

inversely correlated with the progression of cardiovascular disease, and this benefit is likely due to the fact that garlic is a rich source of sulfane sulfur^{4a}. Synthetic hydrogen sulfide donors can remarkably protect mitochondria in endothelial cells from oxidative damage^{5a}. All of these examples point to the hypothesis that impaired sulfur supply to the vasculature is the key factor in cardiovascular disease.

Cholesterol Sulfate Synthesis in the Skin

Geographical data show an inverse relationship between cardiovascular disease and annual sunlight availability⁶. In a study conducted in the British Isles, 49% of the variance in mortality from coronary heart disease was accounted for by mean annual sunshine hours⁷. However, despite the fact that vitamin D deficiency is associated with cardiovascular disease risk⁸, placebo-controlled trials have failed to show any benefit from vitamin D3 supplementation⁹.

We suggest that the benefit comes from cholesterol sulfate synthesis instead. In^{10a}, it was proposed that sulfate is produced from reduced sulfur sources in the skin, catalyzed by sunlight. The enzyme that likely carries out this function was identified as endothelial nitric oxide synthase (eNOS), the same enzyme that produces nitric oxide to relax the artery wall. We hypothesize that the overuse of sunscreen has played a dual damaging role not only because sunlight catalysis is suppressed but also because the aluminum in high-SPF sunscreens actively disrupts eNOS' function, due to displacement of the iron in the heme group¹¹. eNOS is a cytochrome P450 (CYP) enzyme, and many other environmental chemicals also disrupt CYP enzymes, including mercury^{12a,13}, arsenic¹⁴, cadmium^{12b}, and glyphosate^{15,16}, the active ingredient in the pervasive herbicide, Roundup.

It is well established that eNOS produces superoxide as well as nitric oxide, but this has always been viewed as a pathology¹⁷. At the same time, the fact that RBCs contain abundant eNOS has always posed a puzzle to biologists, because nitric oxide would disrupt hemoglobin's ability to transport oxygen¹⁸. But if the superoxide synthesis by eNOS represents an alternative function to oxidize sulfur, then both of these puzzles are explained. Thiosulfate, derived from hydrogen sulfide gas via oxidation in

the mitochondria, may be the primary source of sulfur that is oxidized by eNOS to ultimately yield two sulfate anions^{10b}.

Correlation does not always imply causation, but it would be surprising for causative factors not to be correlated with the disease they cause. Most people assume that elevated serum lipids are a causal factor in coronary artery disease (CAD). Therefore, a plot over time of the hospital discharge rates for hyperlipidemia should be highly correlated with a similar plot for CAD.

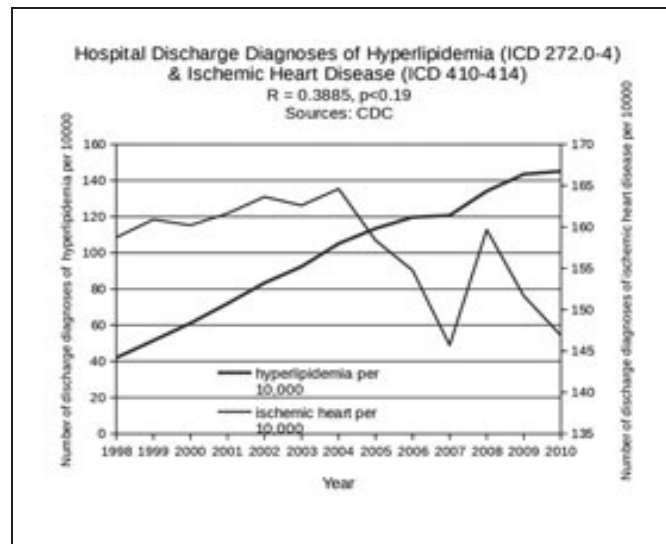


FIGURE 1 Graph of incidence of hospital discharge diagnoses of hyperlipidemia (ICD 272.0- 4) and ischemic heart disease (ICD 410-414) over time from 1998 to 2010, available from the CDC.

As Figure 1 shows, this is not the case. The correlation value is 0.39 with an insignificant p-value of 0.19. Yet, tens if not hundreds of millions of people are advised by their doctor to take a statin drug to protect them from CAD because their serum lipid levels are high.

There is a much stronger, highly significant, correlation between hyperlipidemia and glyphosate application to corn and soy crops: $R = 0.97$, and $p < .000018$, as shown in Figure 2.



FIGURE 2 Graph of incidence of hospital discharge diagnoses of hyperlipidemia (ICD 272.0-4), available from the CDC, and the rate of glyphosate application to corn and soy crops, obtained from the US Department of Agriculture.

Glyphosate application rates have steadily increased over time due to the widespread appearance of glyphosate resistant weeds growing among the crops that are increasingly engineered to be glyphosate resistant. Serum lipids have also risen in step with this increase in glyphosate, despite the increase in statin drug prescriptions.

It is not unreasonable to propose that glyphosate is causal in hyperlipidemia. Glyphosate disrupts CYP enzyme activity in the liver^{19a}, and multiple CYP enzymes are needed to produce bile acids²⁰. Bile acids contain sulfated oxysterols derived from cholesterol through the action of CYP enzymes, which eventually make their way into chylomicrons that enter the lymph system from the gut and exit into the vascular system in the large veins feeding directly into the heart. Thus, normally, bile is a major source of sulfated sterols to supply the heart.

A rat study assessing the impact of glyphosate, clofibrate and two phenoxyacid herbicides on liver function showed that glyphosate reduced the activity of CYP enzymes in the liver much more than any of the other pesticides investigated^{19b}. Bile acids normally export a large amount of cholesterol via the digestive system, most of which is reabsorbed via the chylomicron. Impeded bile acid synthesis due to a defective CYP7A1 gene produced neonatal cholestasis and hypercholesterolemia, specifically,

elevation in serum LDL, in mice fed a normal chow diet²¹.

It is plausible that glyphosate also disrupts eNOS' ability to synthesize sulfate, given that eNOS is also a CYP enzyme. Glyphosate exposure to eNOS in RBCs is expected, as glyphosate export via the kidney requires transit through the vasculature. Disrupted synthesis of cholesterol sulfate, both through the impaired activity of bile acid enzymes and through eNOS dysfunction, will necessitate an increase in the synthesis of LDL particles to transport cholesterol in the unsulfated form, which is hydrophobic.

Furthermore, glyphosate likely disrupts the metabolism of fructose by gut microbes, due to its impairment of the shikimate pathway²². This places a huge burden on the liver to metabolize fructose to fat, which then needs to either be stored locally, inducing fatty liver disease, or exported within lipid particles. Fructose is a major factor in non-alcoholic fatty liver disease (NAFLD) and the metabolic syndrome²³. Fatty liver disease has become an epidemic worldwide²⁴. Furthermore, NAFLD is a strong risk factor for cardiovascular disease²⁵.

The Atheroma Supplies Cholesterol Sulfate

Davidson et al.²⁶ proposed that RBCs produce cholesterol sulfate while traversing the surface veins, catalyzed by sunlight, and release it to the tissues in the capillaries. This refurbishes both the cholesterol and the sulfate supply to the endothelial wall, maintaining vascular health. Heparan sulfate proteoglycans (HSPGs) in the glycocalyx play many important roles²⁷, mediating cellular signaling mechanisms and promoting uptake of various nutrients, including LDL clearance by hepatocytes²⁸. But perhaps the most important role in the capillary is to maintain a thick layer of gelled water coating the inner surface. This structuring effect on water is due to the kosmotropic properties of sulfate²⁹. It provides a near-frictionless surface contact with the RBCs^{10c}, that is further enhanced by the negative charge in both the glycocalyx and the RBC membrane. As the RBC drops off cholesterol sulfate, it also loses negative charge, which means that the venous end has a lower pH than the arterial end. An increase in carbon dioxide content on the venous side enhances this effect, as is extremely apparent immediately following cardiac arrest, when CO₂ accumulates in

the veins and the voltage difference between arteries and veins is sharply increased³⁰. Thus, an electrical gradient also propels the negatively charged RBC through the capillary. Capillary resistance is the dominant factor in high blood pressure, which can therefore be expected to correlate with an impoverishment in cholesterol sulfate in RBC membranes and heparan sulfate in the capillary wall. Both increased friction at the walls and decreased force from the electromagnetic field contribute to impeded movement of RBCs through the capillary³¹.

The glycocalyx is constantly shed and rebuilt in a dynamic process that is promoted by inflammatory agents³². Complement and endotoxin both induce glycocalyx shedding through a G-protein coupled receptor response. Such matrix remodelling is especially active during ischemia/reperfusion. Membrane-bound matrix metalloproteinases can detach fragments of the glycocalyx from the artery wall which can then be redistributed to other parts of the vasculature, such as the capillaries, as reinforcements. Thus, it is highly conceivable that the glycocalyx in atherosclerotic regions is a source of raw materials needed to maintain the health of the HSPGs in the capillary glycocalyx.

The atheroma is uniquely suited to the manufacture of cholesterol sulfate by platelets, where the sulfate is supplied by breaking down homocysteine thiolactone, the cholesterol is supplied from the lipid stores in the macrophages, ATP to energize the reaction is supplied by red blood cells, and superoxide, needed to oxidize the sulfur atom in homocysteine, is provided through the inflammatory response^{10d}. HDL plays a critical role, because platelets will only take up cholesterol from HDL-A1 (the “good” variant), and they will increase their production of cholesterol sulfate 300-fold in the presence of 3’-phosphoadenosine-5’-phosphosulfate (PAPS), a source of transferrable sulfate produced by sulfation of ATP³³. ApoE plays a significant role as well, as it induces the export of cholesterol from the macrophages into HDL-A1, but it also induces enrichment of sulfate in the HSPGs³⁴. This implies that it escorts cholesterol sulfate out of the cell rather than cholesterol. This idea is also supported by the fact that cholesterol sulfate, unlike cholesterol, is water soluble, and therefore readily traverses the cytoplasmic gap between the endothelial reticulum and the plasma membrane. Both homocysteine³⁵ and gamma-

glutamyltransferase (GGT)^{36a,37} are risk factors for heart disease, and both can be explained because they provide substrate for sulfate synthesis. GGT breaks glutathione down into cysteinylglycine and glutamate, and cysteine from cysteinylglycine can be oxidized to form sulfate³⁸.

The atheroma harbors various microbial infections, the most significant of which is probably *Chlamydia pneumoniae*^{39,40a}. While the concept of antibiotic treatment specific to *C. pneumoniae* was enthusiastically embraced, clinical trials have been disappointing⁴¹. *C. pneumoniae* are dormant except when internalized into host cells, and, within these cells, they produce a unique form of heparan sulfate, using a set of enzymes that are not found in any other known species⁴². I hypothesize that they play a special role in enhancing the supply of heparan sulfate to the atheroma, and they may be able to do so in the absence of functional CYP enzymes.

A Role for PCSK9

Cholesterol sulfate, along with its close cousin, dehydroepiandrosterone (DHEA) sulfate, is the most common sterol sulfate in the blood⁴³, and it will readily enter any lipid membrane, including the lipid monolayer of the suspended LDL and HDL particles. I hypothesize that it serves a protective role in preventing oxidative and glycation damage to these particles. The “small dense LDL particles” are the most atherogenic, and they arise because glycation and oxidation prevents the reuptake and recycling by the liver.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proprotein convertase that is synthesized mainly by hepatocytes in the liver. When present in the cytoplasm of hepatocytes, it binds to the LDL receptors and causes them to be metabolized, resulting in reduced liver uptake of spent LDL particles, thus raising serum LDL levels^{44a}. However, after it is glycosylated and tyrosine-sulfated in the golgi, PCSK9 sulfate is secreted⁴⁵, and, once in the serum, it binds to LDL particles⁴⁶. Thus it can be hypothesized that PCSK9 serves a protective role similar to that of cholesterol sulfate in preventing LDL particles from becoming oxidized and glycated, through the structuring effects of sulfate on water. It may also be the case that accumulation of unsulfated PCSK9 in the cytoplasm is an

indicator of either sulfate deficiency or impaired sulfotransferase capacity. Statin drugs induce an increase in PCSK9 synthesis⁴⁷. It can be conjectured that reduced supply of cholesterol sulfate necessitates increased supply of tyrosine sulfate to compensate.

It appears then that, when sulfation capacity is impaired in hepatocytes, poorly protected LDL particles accumulate in the serum due to the loss of LDL receptors in the liver. These vulnerable LDL particles are then oxidized and taken up by macrophages in the atheroma, where their contents become substrate for cholesterol sulfate synthesis. There is considerable enthusiasm for a new class of monoclonal antibody drugs that interfere with PCSK9 function on the LDL receptor^{44b}. A single injection of monoclonal antibodies to PCSK9 resulted in a greater than 60% drop in LDL cholesterol, due to enhanced reuptake by the liver. I predict that these drugs will cause some unexpected consequences both because LDL particles will be more vulnerable to attack by oxidizing and glycation agents, due to loss of protection from PCSK9, and because the liver will try to recycle more cholesterol than it can safely dispose of through the bile acids, which may lead to fatty liver disease. The impaired sulfation capacity that PCSK9 should be signaling will still exist even though there is insufficient PCSK9 to adequately signal the problem.

Cholesterol Sulfate and Leukotrienes

Arachidonic acid (AA), produced by polymorphonuclear cells (PMNLs), is a key stimulating factor in the inflammatory cascade that leads to allergy, asthma and atherosclerosis^{48,49}. The first step in this cascade is the conversion of AA to leukotriene A₄, mediated by the highly regulated enzyme 5-lipoxygenase (5-LO). The 5-lipoxygenase pathway has been implicated in the pathogenesis of atherosclerosis^{50,51}. 5-LO is activated by calcium influx, which induces its binding to the nuclear membrane⁵².

Cholesterol sulfate has a profound inhibitory effect on 5-LO, which likely depends on its internalization and trafficking to the endoplasmic reticulum⁵³. Membrane fluidity is a key modulator of the activity of 5-LO, and cholesterol decreases the permeability of membranes, thereby decreasing fluidity^{54,55,56}. I hypothesize that the sulfate anion provided by

cholesterol sulfate mobilizes the cholesterol in the ER, such that it can now populate the nuclear membrane and inhibit the activity of 5-LO. I further hypothesize that the conversion of AA to leukotrienes is a key mechanism by which PMNLs signal cholesterol sulfate deficiency, in order to provoke a system-wide inflammatory response that will restore sulfate supplies to the vasculature, through oxidation of sulfur in homocysteine or cysteinylglycine by superoxide, thereby mobilizing cholesterol.

Chagas Syndrome, Down Syndrome and Statin Drugs: Multiple Pathways to Heart Failure

Deaths from MI have steadily decreased in the industrialized world over the past few decades^{57,58}, but we are simultaneously experiencing an increasing health care burden in an emerging epidemic in heart failure⁵⁹. In fact, heart failure is the single most frequent cause of hospitalization for those over 65 years old, affecting 5 million Americans as of 2010⁶⁰. I maintain that heart failure is a direct sequela to insufficient supply of cholesterol and sulfate to the heart. Since the atheroma plays a significant role in supplying these nutrients, it can be anticipated that factors that interfere with the healthy function of the atheroma will lead over time to heart failure.

Chagas syndrome is an infectious disease endemic to regions of South America caused by the *Trypanosoma cruzi* pathogen^{61a,62a}. Recovered patients are susceptible to premature death by heart failure many decades later. However, they have been noted to be remarkably free of atherosclerosis, although they suffer from frequent small heart attacks^{62b}. The explanation for this unique profile follows logically from the fact that *T. cruzi* produces an antigenic molecule that closely mimics cholesterol sulfate^{61b}. As a result, these patients develop antibodies to cholesterol sulfate, which would render the synthesis of cholesterol sulfate by the atheroma counterproductive, but lead to system-wide deficiencies in cholesterol and sulfate.

Down syndrome (trisomy 21) is associated with a low risk to atherosclerosis^{63,64} combined with a premature susceptibility to heart failure⁶⁵ and Alzheimer's disease (AD)⁶⁶. A key enzyme present on chromosome 21 is Cu/Zn superoxide dismutase (SOD), which is thus 50%

overexpressed in association with Down syndrome⁶⁷. SOD dismutates superoxide to hydrogen peroxide, thus reducing the bioavailability of superoxide for the oxidation of reduced sulfur sources, such as homocysteine thiolactone and cysteinylglycine (derived from glutathione)^{36b}, to form sulfate. Downs patients are susceptible to AD at least 20 to 30 years earlier than is normally expected, and dementia is clinically detected in association with Down syndrome at least 3 times more frequently than in those without trisomy 21⁶⁸. Sulfate deficiency likely plays a significant role in the AD brain, as evidenced by the severe deficiency in sulfatide, the only sulfonated lipid, observed in association with AD⁶⁹.

Many have argued that statin drugs produce their pleiotrophic effects through an anti-inflammatory effect^{70,71,72}, and, further, that other treatments aimed at reducing inflammatory signaling might be effective treatments⁷³. I predict that both statin therapy and these other treatments will lead to heart failure. Statins also disrupt G- protein coupled receptor signaling via their suppression of the synthesis of geranylgeranyl pyrophosphate, leading to defective protein prenylation⁷⁴, which explains their induction of arterial calcification⁷⁵. Thus, I propose that statin drugs promote heart failure through impairment of cholesterol sulfate synthesis in the atheroma, both by reducing the bioavailability of LDL to the atheroma and by interfering with the inflammatory response. Not surprisingly, low cholesterol is consistently associated with poor survival statistics in heart failure^{76a,77a,78a}. In heart failure, total cholesterol levels under 200 mg/dl increase risk of dying by up to 3 fold^{76b,77b}. Fonarow et al. state, provocatively: “Could elevated total cholesterol, which is so firmly established to be deleterious for the development of coronary heart disease and coronary heart disease mortality, actually turn out to be good for patients with chronic HF?”^{78b}, p. 1941.

Does Taurine Replenish Sulfate in MI?

Taurine (aminoethanesulfonic acid) is the only sulfonated amino acid, and its roles in the body are yet to be fully clarified. The highest concentrations of taurine are found in the heart, and taurine represents 50% of the free

amino acid pool there⁷⁹. Although some bacteria can utilize taurine as a fuel source^{80a}, it has long been maintained that taurine can not be metabolized by mammalian cells. However, reperfusion injury following coronary bypass surgery is decreased by preoperative infusion of taurine⁸¹, and taurine supplementation improves heart function following MI in rat studies⁸².

Taurine clearly plays a critical though poorly understood role in cardiovascular disease. It is stored in large concentrations in the brain, heart and liver, and it is also retained in blood platelets. Acute left ventricular ischemia in the dog as well as whole heart anoxia in the rat heart in vitro resulted in the disappearance of taurine from the left ventricle via leakage into the extracellular fluid⁸³. Studies on dogs, cats and humans have demonstrated a direct linear relationship between plasma taurine levels and platelet taurine levels^{84,85a}. Platelets from taurine deficient cats and humans are more sensitive to clotting stimuli^{85b}. Early studies in dogs showed that taurine was mainly concentrated in the atria, and ischemia induced a 47% loss of taurine in the left ventricle and a 26% loss in both atria⁸⁶.

Human polymorphonuclear leukocytes (PMN) produce myeloperoxidase (MPO) during ischemia/reperfusion injury⁸⁷, and elevated MPO is an established risk factor for cardiovascular mortality following angiography⁸⁸. Since MPO often serves as a potent bacteriocidal weapon⁸⁹, it potentially links to the infectious theory of heart disease^{90a,40b}. Hypochlorite (HOCl), produced in response to MPO, avidly oxidizes many sulfhydryl-dependent proteins, leading to platelet activation and endothelial adhesion by neutrophils, and it has been proposed that taurine protects from these damaging effects by reacting with and neutralizing HOCl to form taurine chloramine⁹¹. As we have seen, taurine is released from the heart during ischemia, and it is not taken up by the platelets⁹², so it would be readily available in the serum. However, taurine chloramine activates complement, by producing a hemolytic C5-C9 complex⁹³. Complement activation, in turn, promotes an inflammatory response, providing oxidizing agents that could in theory promote the oxidation of sulfur in taurine chloramine.

Thus, a novel way to view taurine is as a potential buffer for sulfate

renewal in times of acute deficiency. If sulfate insufficiency is an important factor in heart disease, an important question to ask is: can taurine chloramine become a substrate for sulfate synthesis? After all, it already contains sulfur at a +5 oxidation state, so it only needs to oxidize it from +5 to +6 to produce sulfate. Taurine chloramine is a much more reactive compound than its precursor, taurine.

Taurine is not easily catabolized by mammalian cells⁹⁴. However, 25% of the traced sulfur in supplemental taurine turned up in the urine as sulfate. The hypothesis was put forward that the gut bacteria metabolized the taurine to sulfate. Since taurine chloramine is more reactive, perhaps it can be metabolized to yield free sulfate, with microbial infective agents playing a facilitative role. If so, this would justify both cardiac storage of taurine as a source of sulfate during times of severe deficiency, as well as the presence of microbes in cardiovascular lesions^{90b,40c}, and it would lend further credibility to the infectious theory of heart disease.

Taurine offers protection during ischemia/reperfusion, although the mechanism has not yet been worked out⁹⁵. There is a severe loss of taurine from the heart during ischemia that can lead to heart failure if the taurine is not replenished. A World Health Organization population study revealed an inverse association between taurine excretion and ischemic heart disease mortality⁹⁶. Reperfusion causes a burst in oxygen consumption through diversion of the electrons from the electron chain into superoxide production^{97,98}. We argue that a key purpose of this superoxide is to oxidize sulfur derived from cysteine or homocysteine from a -2 oxidation state to a +6 oxidation state, producing sulfate from sulfide and consuming two superoxide anions. Several enzymes working in conjunction with the mitochondrial electron chain are involved in oxidizing H₂S to sulfate and thiosulfate⁹⁹. As described in¹⁰⁰, homocysteine thiolactone is converted to sulfate in the presence of superoxide, catalyzed by vitamin A and vitamin C, possibly explaining the positive role of vitamin C in protection from cardiovascular disease¹⁰¹.

Taurine offers many health benefits to the cardiovascular system¹⁰². Taurine has been shown to inhibit the osteoblastic differentiation of vascular smooth muscle cells that leads to artery calcification¹⁰³. Taurine showed protection against the loss of mechanical function in rat hearts in

both a heart failure and ischemia model¹⁰⁴. In particular, taurine suppresses the production of superoxide during reperfusion¹⁰⁵. We propose here that this suppressive effect is achieved mainly due to the fact that it contains sulfur already at a +5 oxidation state, and hence only 1/6 as much superoxide is needed to produce an equivalent amount of sulfate. The fact that taurine is normally inert makes it a great choice for buffering as a precursor to sulfate. However, HOCl is needed to convert it into the more reactive molecule, taurine chloramine, from which sulfate can be derived, with the help of superoxide and perhaps microbial enzymes. Species of *Clostridium* are able to utilize sulfonate forms of sulfur, such as taurine, as an energy source, and, more generally, it has been confirmed that anaerobic bacteria can convert taurine directly to thiosulfate^{80b}.

Experiments have confirmed that taurine can be broken down to sulfoacetaldehyde by neutrophils, with taurine chloramine as an intermediary, through nonenzymatic hydrolysis catalyzed by hydrogen peroxide¹⁰⁶. With an adequate source of energy, sulfoacetaldehyde can react with phosphate to produce acetyl phosphate and sulfite. Sulfite can then be oxidized to sulfate via enzymatic action of sulfite oxidase. We propose that this reaction takes place during MI. A China-based study of possible associations between biochemical, diet, and lifestyle factors and cardiovascular disease did not find any relationship with serum cholesterol, but showed a protective effect for molybdenum¹⁰⁷. This could be explained by the fact that molybdenum is a cofactor for sulfite oxidase.

It is possible that a resonance phenomenon in structured water plays a role. Del Giudice et al.^{108a} argue that coherent oscillation of almost-free electrons in water molecules within an exclusion zone surrounding a kosmotropic hydrophilic surface can become a source of free electrons for chemical reactions. The water molecules are resonating in tune with an electromagnetic field, and they serve to capture energy within the exclusion zone to excite and mobilize electrons. The Schumann resonance frequency of the earth's geomagnetic field at 7.83 Hz is a possible source. It has been suggested that low frequency (< 10Hz) alpha waves in the brain are influenced by geomagnetic pulsations in the ionosphere ranging from 0.1 to 10 Hz¹⁰⁹. It has also been argued that encephalopathy is a mechanism to renew sulfate supplies to the brain, by metabolizing taurine to sulfate, using

seizures as a source of energy to induce resonance phenomena in the structured water¹¹⁰. So, here we are suggesting an analogous mechanism in the heart.

Atrial fibrillation (AFIB) is a frequent occurrence in the context of MI, particularly in the elderly¹¹¹. Frequency analysis of recordings made during AFIB reveal a peak frequency response in the range of 5 to 7 Hz^{112, 113}. We propose that low frequency energy generated by cardiac arrhythmia, analogous to similar low-frequency stimulation from seizures, may serve as an energy source to create such coherence domain oscillations within the water at the surface of certain cell types within the heart, providing energy needed to produce sulfate from taurine. Clearly, much more research is needed to explore these possibilities.

Cardiovascular Disease Prevention and Treatment

If the ideas proposed here are valid, they suggest some very simple measures that can be taken to decrease the risk of cardiovascular disease. Consuming a strictly organic diet that is rich in sulfur-containing foods and spending significant time outdoors without sunscreen on sunny days are two important lifestyle changes. Many sulfur-containing compounds have been shown to benefit cardiovascular health. Garlic, an excellent source of sulfane sulfur, has been consistently recognized as a healthy supplement^{4b,114}. α -Lipoic acid is cardioprotective¹¹⁵, and its benefit may derive from its ability to increase sulfane sulfur levels and rhodanese activity in the heart, liver and kidney¹¹⁶. Chondroitin sulfate and glucosamine sulfate reduce the levels of inflammatory markers such as interleukin 1 β ¹¹⁷, and this may well be mainly because they are a source of sulfate. The synthetic chemical, AP39, has been shown in rat studies to supply hydrogen sulfide gas to mitochondria and protect them from DNA oxidation damage^{5b}. It may therefore be a promising future prevention/treatment option for humans. Vanadyl sulfate is cardioprotective¹¹⁸. This may be mainly due to its ability to supply sulfate, as its sulfate anion dissociates rapidly in solution. N-acetyl cysteine has shown significant benefit during acute myocardial infarction, through multiple effects including reduction in oxidative stress, more rapid

reperfusion, better left ventricular preservation and function, and reduced infarct size¹¹⁹. A placebo-controlled experiment on magnesium sulfate supplements during acute myocardial infarction revealed a 24% relative reduction in all-cause mortality and a 25% relative reduction in left ventricular failure in the treatment group¹²⁰. Is it possible that the sulfate rather than the magnesium is the critical beneficial factor? Thus, a broad range of biologically active molecules that have been recognized as being cardioprotective have in common the feature that they supply sulfur to the body.

The Body Electric

While the topic of electricity in the body is beyond the scope of this chapter, I want to leave you with an image of a solar-powered electrical circuit connecting all parts of the body, where the “wires” are the blood vessels. The biosulfates in the glycocalyx play an essential role in maintaining an “exclusion zone” of gelled water lining all the vessel walls, within which electrons are mobilized in the gel and protons at the interface to produce electrical current that powers the muscles and neurons^{108b,121,122}. Thus, cholesterol sulfate captures sunlight energy in the bound sulfate anion to fuel both mobility and neuronal signaling, just as chlorophyll endows plants with the ability to convert sunlight energy into stored sugars, starches, and fats. Life on the earth’s surface has always had access to sunlight as an energy source, and animals and plants have found distinct ways to utilize it.

Sunlight is used by animals to oxidize oxygen to superoxide, and then to oxidize sulfur to sulfate. Cholesterol is the carrier molecule that distributes the sulfate over the vasculature. It too is oxidized by sunlight to form vitamin D, a signaling molecule that communicates to the tissues that all is well. As the negatively charged RBC traverses the capillary, it creates a dynamic electromagnetic signal called the “streaming potential” that oscillates with the rhythm of the heart beat. Endothelial cells respond to this signal by releasing nitric oxide, which relaxes the vessel and promotes flow¹²³.

Conclusion

In this chapter, I have proposed a hypothesis that explains the complex processes that take place in the atheroma as a mechanism to assure cholesterol sulfate supplies to the heart. Cholesterol sulfate is an important source of sulfate to maintain the RBCs' negative surface charge and to populate the extracellular matrix of the endothelial wall. This results in near frictionless trafficking of RBCs through capillaries. I maintain that the modern lifestyle of sun avoidance and exposure to toxic chemicals through food, sunscreen or other environmental insults results in impaired cholesterol sulfate synthesis in the skin mediated by sunlight. This pathology necessitates a mechanism to store cholesterol in the artery wall to be made readily available for cholesterol sulfate synthesis whenever sulfur sources such as homocysteine or cysteinyl-glycine are available, along with superoxide and ATP as sources of oxygen and energy to fuel the reaction. In an emergency, a myocardial infarction can initiate a programmed response that depletes taurine reserves to restore sulfate supplies. Microbes such as *C. pneumoniae* can assist in replenishing heparan sulfate to the artery wall. I argue that statin therapy interferes with cholesterol sulfate production, leading to increased risk to heart failure, which is now a major contributor to rising health care costs.

If the ideas contained in this chapter are widely embraced, the field of cardiovascular disease treatment will be revolutionized. Patients will be encouraged to spend significant time outdoors on sunny days without sunscreen, and will be encouraged to eat a diet consisting of organic whole foods that are rich in sulfur content. Nutritional supplements that contain sulfur, such as α -lipoic acid, N-acetyl cysteine, garlic extract, chondroitin sulfate, etc., will be prescribed by doctors. Statin drugs will become a thing of the past, because it will be recognized that any benefit they provide in terms of reduced rate of myocardial infarction are completely offset by the serious side effects incurred because of the further depletion of the supply of cholesterol sulfate to the tissues. It will finally be acknowledged that statin therapy is a poor option in heart disease prevention.

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Chapter Ten

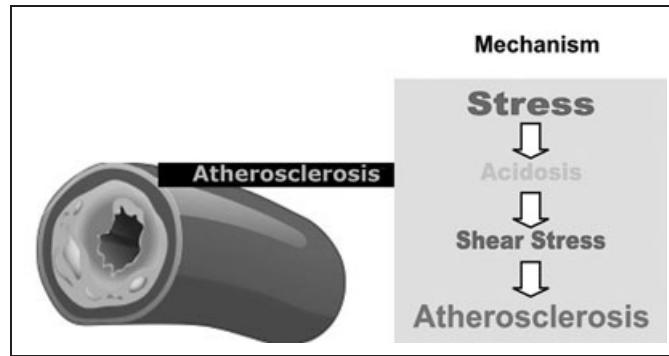
Stress as Cause of Atherosclerosis:

The Acidity Theory

Carlos E. T. B Monteiro

Abstract

The link between stress and atherosclerosis is well-known with many studies and postulations in this regard. However, there is a general unawareness that stress can induce hyperlactatemia and lactic acidosis, because this relationship has been little discussed in medical science. The influence of adrenaline on lactic acid production was first noticed by Carl Ferdinand Cory in 1925. The heart is an organ of high metabolic activity – that cannot rest as other body muscles, being susceptible to drops in pH during ischemia and hypoxia. The chronic elevated catecholamine release, triggered by sympathetic dominance, may accelerate the myocardial glycolysis leading to significant increase in lactate production. Risk factors for atherosclerosis like hypertension, diabetes, cigarette smoking, stress conditions and high carbohydrate diets are linked to autonomic dysfunction. These risk factors present as well an increased concentration of lactate in plasma. Blood lactate is also associated with carotid atherosclerosis. Plasma lipid abnormalities and myocardial lactate production were significantly associated with subsequent arteriographic progression. The amount of lactate released by the myocardium has been shown to be related to the severity of coronary artery disease. Reduced pH increases the oxidation of low-density lipoprotein that is considered to have a significant role in atherogenesis. According to the acidity theory of atherosclerosis the acidosis evoked by sympathetic dominance or continuous stress leads to changes in shear stress, the final stage in the development of atherosclerotic lesions. The importance of mechanical forces such as those derived from changes in hemodynamic shear stress, as a decisive factor for atherosclerosis, was advocated by Meyer Texon since 1957.



Introduction

In a recent article we presented the history about the acidity theory of atherosclerosis, developed in 2006, addressing its pathophysiology, therapeutics, risk factors and external markers. There I also have wrote about individuals with lower degree or absence of atherosclerosis, and on the reversion or lower progression of atherosclerosis through the use of sympatolytic drugs and by stress reduction approaches¹. In the current article I extend the discussion about the etiology of the Acidity Theory of Atherosclerosis, aside to present new risk factors and other diseases associated to atherosclerosis, under its point of view. Also, I bring up for discussion the inverse association between cancer and atherosclerosis, confirmed by recent studies.

Our hypothesis

The myogenic theory^{2a}, developed by Dr. Quintiliano H. de Mesquita, from Brazil, became the template for the acidity theory of atherosclerosis. In his point of view the heart disease process involves two distinct pathologies, one for coronary artery disease/atherosclerosis and other for the myocardial disease, what led to his adoption of the terms “coronary-cardiomyopathy” or “coronary-myocardial disease”, instead “coronary heart disease” and the term “acute myocardial syndromes” instead “acute coronary syndromes”. His reasoning was contrary to the currently accepted thinking which has its cause and effect relationship based in the thrombocentric coronary heart disease model.

Noteworthy is the citation from Dr. George E Burch, a shaper of modern cardiology, which goes strikingly to the point:

“The coronary patient does not die from coronary disease, he dies from myocardial disease.”
(1972)³

Our acidity theory of atherosclerosis fits perfectly well with the myogenic theory of myocardial infarction. The myogenic theory accepts that physical and emotional stresses affect the cardiac muscle dependent on the diseased coronary artery, compromising the myocardial structure. In his book about the myogenic theory from 1979, Dr. Mesquita says: “Thus, the coronary disease contributes to the deterioration of the ventricular segment, constituting areas of myocardial sclerosis or segmental myocardial disease, the possible future site of the myocardial infarction”.⁴

Acidity Theory of Atherosclerosis Mechanism

- I. Sympathetic dominance by continuous stress plus
- II. Deficiency in production of endogenous digitalis-like compounds with alterations of Na(+), K(+)-ATPase activity results in:
- III. Lowered pH (acidosis) that increases perfusion pressure and provokes effects on contractility of coronary arteries leading to changes in hemodynamic shear stress and atherosclerosis as consequence.

The sequence of events to explain atherogenesis, in the acidity theory concept

Fundamentals

Stress and Acidosis

The heart is an organ of high metabolic activity – that cannot rest as other body muscles, being susceptible to drops in pH during ischemia and hypoxia. The chronic elevated catecholamine release, triggered by sympathetic dominance, may accelerate the myocardial glycolysis leading to significant increase in lactate production. According to a study from 1982 the support for a direct participation of catecholamines in the development and/or maintenance of lactic acidosis includes: 1) the common association of stress and lactic acidosis; 2) the rise in plasma lactate concentration during adrenaline infusion; 3) the precipitation of lactic acidosis by adrenaline intoxication and phaeochromocytoma; and 4) the

vasoconstrictor effects of catecholamines leading to tissue anoxia and lactic acid production⁵

The influence of adrenaline on lactic acid production was first noticed by Carl Ferdinand Cory in 1925^{6a}. Together with his wife Gerty Cory, received a Nobel Prize in 1947 for their discovery of how glycogen– a derivative of glucose – is broken down and resynthesized in the body. John R. Williamson confirmed in 1964 the effects of adrenaline infusion on the increased production of lactate in isolated heart tissue, up to five times the normal production⁷. (Note: Lactic acidosis results from increased production of lactate, the final product in the pathway of glucose metabolism. Lactate and lactic acid are not synonymous. Lactic acid is a strong acid which, at physiological pH, is almost completely ionized to lactate)

Hyperlactataemia is common during physiological (exercise) and pathophysiological stress^{8*}

Risk factors for atherosclerosis like hypertension^{9,10}, diabetes^{11,12}, cigarette smoking¹³, stress conditions^{14,15} and high carbohydrate diets^{16,17} have shown an increased concentration of blood lactic acid or lactate.

Blood lactate is also associated with carotid atherosclerosis^{18a}.

Lowered pH increases perfusion pressure^{19,20,21a}. Also, pH changes have profound effects on contractility of coronary arteries^{21b,22}, that may happen through the sodium/potassium pump and K induced relaxation channels²³.

The association of increased lipid levels with abnormal lactate metabolism may provide a useful screening test for the detection of coronary artery disease. It was found that plasma lipid abnormalities and myocardial lactate production were significantly associated with subsequent arteriographic progression. The amount of lactate released by the myocardium has been shown to be related to the severity of coronary artery disease.^{24,25,26}

Additional findings linking lactate/lactic acid and atherosclerosis

1. In advanced plaques the existence of hypoxic areas in the arterial wall – with accumulation of lactic acid in atherosclerotic lesions – seems to be related to a decreased oxygen diffusion capacity and increased

oxygen consumption by the foam cells²⁷

2. A pathological study has demonstrated that approximately two-thirds of the atherosclerotic plaques show lactate dehydrogenase isoenzyme shifts significantly above the media and intima²⁸.
3. Macrophages and lymphocytes convert most of their glucose into lactate rather than oxidizing it completely to CO₂, and macrophages possess a selective transporter in their plasma membranes for lactic acid. This lactic acid may make the extracellular space surrounding macrophages acidic in atherosclerotic lesions^{29a}
4. Lowering pH augments the oxidation of low-density lipoprotein (LDL) by releasing Fe and Cu radicals and decreasing anti-oxidant defense capacity^{29b,30,31}
5. LDL oxidation occurs not within the interstitial fluid of atherosclerotic lesions but within lysosomes in macrophages in atherosclerotic lesions. The study also found that this oxidative modification was inhibited by the drug chloroquine, which increases the pH of lysosomes, as oxidation can be promoted by acidic pH³²
6. In-vitro findings suggest that in areas of atherosclerotic arterial intima, where the extracellular pH is decreased, binding of apolipoprotein B100 containing lipoproteins to proteoglycans and modification of the lipoproteins by acidic enzymes are enhanced. The pH induced amplification of these processes would lead to enhanced extracellular accumulation of lipoproteins and accelerated progression of the disease^{33,34}
7. The acidic environment also represents a novel endogenous danger signal alerting the innate immunity. Low pH may thus contribute to inflammation in acidosis-associated pathologies such as atherosclerosis.³⁵

Endogenous digitalis like compounds, the sodium potassium pump and cardiac glycosides

There is a postulation that epinephrine (adrenaline) increases lactate formation by a raise in the Na⁺K⁺ ATPase activity. This can be inhibited through digitalis or strophanthin/ouabain which are sodium pump inhibitors.³⁶ The link between adrenaline and increased Na⁺K⁺ – ATPase activity is well established.

Endogenous digitalis-like compounds of the cardenolide (digoxin and ouabain / strophanthin) and bufadienolide (Proscillaridin-A and Marinobufagenin) types, isolated from human tissues and body fluids, have similar molecular structure of cardiac glycosides extracted from plants and toad venom^{38,39a}. Endogenous DLCs are steroidal hormones that are synthesized in, and released from the adrenal gland, whose regulation may be directed by the hypothalamic-pituitary-adrenal (HPA) axis.^{40,41a}

Endogenous DLCs may serve as effectors of ion-transport activity mediated by their interaction with Na,K-ATPase and thus play a role as a new hormonal axis^{37a}

Many hormones, including aldosterone, insulin, thyroid hormone and catecholamines regulate not only the expression but also the insertion of Na⁺, K⁺-ATPase into the plasma membrane, according to specific physiological needs. The Na⁺, K⁺-ATPase which was considered to be the ion transporting pump now appears to have many other unrelated functions, some of which may be regulated by DLCs. In fact DLCs have already been implicated in the regulation of several major physiological parameters including water and salt homeostasis^{39b}

Perturbation of the endogenous digitalis-like compounds system has been implied in many pathological conditions including cardiac arrhythmias, hypertension, heart failure, cancer and depressive disorders.^{39c,42} Stress situations may affect the release of endogenous DLCs by the adrenal gland.^{41b} Also, the extracellular acidification may affect the signaling and transport of endogenous DLCs.^{43,44} This raises the possibility that an insufficient production of endogenous DLCs to attend the demand in some medical conditions, like in coronary-myocardial disease, hypothetically can be resolved through the use of cardiac glycosides at low concentration. This is confirmed by clinical studies using digitalis and strophanthin/ouabain drugs with largely positive effects in prevention of acute myocardial syndromes and mortality.^{2b,45} Low therapeutic doses of digitalis and

strophanthin/ouabain drugs have specific sympathoinhibitory response by blocking the overproduction of catecholamine^{46,47} that may induce a potent inhibition of glycolysis.⁴⁸ We hypothesize that endogenous digitalis-like compounds may have similar action on neurohormonal levels.

Sympatholytic properties from cardiac glycosides (digoxin, digitoxin, ouabain, etc) show positive effects for atherosclerosis including the reduction in plasma levels of total cholesterol, LDL cholesterol and triglycerides. It should take in consideration the fact that stress and other risk factors for atherosclerosis causes the elevation of these elements in blood. Benefic effects of cardiac glycosides are also seen through anti-inflammatory pathways.^{49,50,51,52,53,76a,95,96,97}.

However, inflammation is a result of an injury, not its cause. Incidentally, there are demonstrations about a pivotal role for the sympathetic nervous system and its neurotransmitters in regulating inflammation.⁹⁹

IMPORTANT POINTS:

1. Despite the ongoing advances and recent controversies related to some details⁵⁴ of endogenous digitalis-like compounds, our basic reasoning expressed since 2006 about its importance in the acidity theory of atherosclerosis, remains unaffected.^{55a}
2. Cholesterol is vital for the human body with use in cell membranes, hormones, neurotransmitters, overall nerve function and, among other properties, as a healing agent to repair tissue injuries what occur in atherosclerosis according our concept.^{56,57,58} Cholesterol is the major precursor of endogenous digitalis-like compounds.^{37b} Therefore, the cholesterol lowering by drugs may affect many functions of the body. Incidentally, a study in humans found that statin therapy can be associated with high blood lactate/ pyruvate ratio suggestive of mitochondrial dysfunction.⁵⁹ Statins, besides presenting trivial beneficial results in preventing mortality, have many adverse effects, including the promotion of coronary calcification during atheroma^{60,61}

Hemodynamic shear stress and atherosclerosis

As the final step in this process the changes in pH may lead to mechanical forces over the coronary blood flow intensifying the damaging action in the development of atherosclerotic lesions.

Atherosclerosis preferentially affects the outer edges of vessel bifurcations. In these predisposed areas, hemodynamic shear stress, the frictional force acting on the endothelial cell surface as a result of blood flow is weaker than in protected regions. Studies have identified hemodynamic shear stress as an important determinant of endothelial function and phenotype⁶².

The pulsatile nature of blood pressure and flow creates hemodynamic stimuli in the forms of cyclic stretch and shear stress. The changes in flow patterns can produce potentially deleterious effects on vascular biology. Lowered shear stress and oscillatory shear stress are essential conditions in atherosclerotic lesion size and vulnerability^{63,64}.

THE LINK BETWEEN SYMPATHETIC DOMINANCE AND CHANGES IN HEMODYNAMIC SHEAR STRESS^{**}

The sympathetic activation with elevation of circulating catecholamine causes coronary vasoconstriction and consequent reduction in blood flow. On the other hand the increased lactate (or decreased blood pH) may evoke vascular smooth muscle relaxation and increase of blood flow. These opposite forces working in sequence - with the sympathetic overdrive leading to metabolic acidosis, in our view, may be reconciled to represent a strong explanation for the occurrence of the resulting abnormal stretching/relaxing of coronary arteries, in different directions, simultaneously, on every heart beat, producing changes in hemodynamic shear stress^{65,66,67}, leading to atherosclerotic disease.

The most important scientific advances by researchers that paved the way for our acidity theory of atherosclerosis:

1. Walter Holbrook Gaskell demonstrated in 1880 that acid solutions have effects on the contractility of heart tissues and vascular smooth muscle, representing an important mechanism for the local regulation

- of blood flow during increased metabolic activity.⁶⁹
2. Rudolph Virchow in 1856 described atherosclerosis as “endarteritis deformans” meaning that the atheroma was a product of vascular injury inducing inflammation within the intima of the artery wall, with cholesterol deposit occurring thereafter⁷⁰
 3. Carl F Cory in 1925 was the first to observe the influence of adrenaline/epinephrine on lactic acid production.^{6b}
 4. Meyer Texon in 1957 postulated that mechanical forces such as those derived from changes in hemodynamic shear stress could cause atherosclerosis.⁷¹
 5. Thomas Zsotér et al have demonstrated in 1961 that reduction of blood pH increases blood flow.^{18b}
 6. James P. Henry and Patricia M. Stephens, in 1977, postulated that chronic stress or the constantly heightened sympathetic-adrenomedullary activity might lead to atherosclerosis and cardiovascular disease*.⁷²
 7. Redford B. Williams, in 1978, postulated that recurrent physiologic actions involving exaggerated heart rate and pressor responses to behavioral stimuli might promote arterial injury via hemodynamic forces such as turbulence and shear stress.⁷³

Risk factors for atherosclerosis/coronary artery disease

In a recent article (1) I have presented 24 risk factors for atherosclerosis where the common denominator is the dysregulation of the autonomic nervous system, related to sympathetic dominance, through sympathetic over-activity or withdrawal of the parasympathetic system, with elevation of catecholamine levels. I take this opportunity to add two risk factor linked to autonomic dysfunction, not previously mentioned.

1. **Trans fatty acids:** Trans fatty acids (TFA) consumption are associated with risk of cardiovascular disease. TFA consumption was also linked

with abnormal heart rate variability that reflects autonomic dysfunction.⁷⁴

2. **Cold exposure:** In most healthy human subjects, cutaneous application of ice water, the cold pressor test (CPT), increases arterial pressure, heart rate, and vascular resistance. For many years, CPT has been used to evaluate sympathetic neural control of the peripheral and coronary circulations in humans. A recent study has linked sympathetic activation-UCP1 axis and cold-associated hyperlipidemia that contributes to cold-induced accelerated development of atherosclerotic plaques in mice. In order to verify the clinical relevance, the authors conducted a pilot experiment by recruiting human subjects to their studies. According them this pilot human study further validates the clinical relevance of their mouse studies with the admission of the fact that only a small number of human subjects were recruited at the time, what might lack a sufficient statistical power to justify a definite conclusion⁷⁵

Other diseases associated to atherosclerosis

1. **Osteoporosis:** Studies show a link between osteoporosis and atherosclerosis. One of these reported that hip fracture is two till five times more common in people with cardiovascular disease than in those with no history of this condition. Interesting is that drugs that reduce the elevated production of lactic acid/lactate in the human body like bisphosphonates and beta blockers not only reduced fracture risk in both men and women but also prevented the development of atherosclerosis. It is worth to mention a postulation from 1978, endorsed by other authors, that the body drawn minerals from the bones to neutralize acid and alkaline challenges.^{76b,77,78}
2. **Vitamin C deficiency:** Studies using guinea pigs demonstrated that ascorbic acid deficiency produces atherosclerosis. To our knowledge there are no studies directly indicating autonomic dysfunction in this condition. However, it is interesting to note that Vitamin C improves baroreflex sensitivity leading to an inhibition of the sympathetic

nervous system. A recent study has demonstrated that intravenous administration of vitamin C reduced cardiovascular adrenergic drive in hypertensive patients. There are also studies showing that intra-peritoneal ascorbic acid greatly inhibits atherosclerosis in guinea pigs. High plasma vitamin C concentrations have been associated with low risk of ischemic heart disease.^{68b,76c,79,80}

- 3. Alzheimer's disease:** Pathological, clinical and epidemiological studies indicate that there is an association between Alzheimer's disease (AD) and atherosclerotic disease, through a chronically lowering brain hypoperfusion. Also, current evidence shows that autonomic dysfunction may be associated with AD. Interesting to note is that the use of sympatholytics (beta-blockers), for the treatment of hypertension resulted in fewer Alzheimer's type brain lesions on autopsy than the use of other hypertensive medications. A recent study confirmed that low cardiac index has been associated with the development of incident dementia and Alzheimer's disease.^{81,82,83,84,85}

Inverse association between cancer and atherosclerosis

Recent findings confirm that atherosclerotic lesions are less pronounced in patients suffering from carcinoma than among non-cancerous persons. Interesting to mention is that cancer and atherosclerosis share some risk factors and molecular pathways – acceleration of glycolysis metabolism, therefore increasing lactic acid/lactate concentration in blood and tissues, worsening cancer and atherosclerotic disease. Like in atherosclerosis there are studies indicating that the autonomic dysfunction is the primary cause of cancer.⁸⁶ On the other hand, some anticancer therapies like chemotherapy, which a recent study found it is related to parasympathetic dysfunction, in addition to promote atherosclerosis show a high risk of cardiovascular morbidity and mortality^{87,88,89,90,91}

Also, there are studies investigating the potential impact of cancer and its therapies on coronary artery calcification. A recent paper by the Multi-Ethnic Study of Atherosclerosis trial has demonstrated an increase in the incidence of coronary artery calcification over time in individuals with cancer compared with non-cancer controls.⁹²

Some epidemiologic studies suggest a positive association between elevated serum cholesterol level and risk for certain cancer types.⁹⁸ As said before I see cholesterol serum elevation as a healing agent to repair tissue injuries, including for cancer

Resting heart rate and all-cause and cardiovascular mortality

Last but not least a recent meta-analysis involving a total of 46 studies with more than a million patients confirms that high resting heart rate is independently associated with increased risk of all-cause and cardiovascular mortality in the general population. Its results suggest the risk is increased by 9% and 8% for every 10 beats/min increment of resting heart rate. According to the authors Higher resting heart rate is a marker of an imbalance between the vagal and the sympathetic tone, and dysfunctional autonomic nervous system, playing a central role in the pathogenesis of numerous adverse health conditions. Also, that a relatively high heart rate has direct detrimental effects on progression of coronary atherosclerosis, on occurrence of myocardial ischemia and ventricular arrhythmias, and on left ventricular function.^{93,94}

Notes

1. Our article published at Positive Health Online (1), November 2015, comprises the following matters:
 1. The history of the acidity theory of atherosclerosis
 2. 24 risk factors where the common denominator is autonomic dysfunction
 3. Individuals with lower degree or absence of atherosclerosis
 4. Reversion or lower progression of atherosclerosis by sympatholytic drugs and stress reduction strategies
 5. External risk markers for atherosclerosis and their relationship with lactic acid or lactate concentration
2. There is additional information on the acidity theory of atherosclerosis

that you may find useful in our short (100 pages) and low cost book from 2012^{76d}, which includes our manuscript from 2008^{55b} Some articles contained in this book: “What causes the elevation of cholesterol levels in blood?”, “Hemodynamic shear stress, calcification and atherosclerosis”, “The positive impact of humor and negative of stress over the vascular function”, etc...

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Chapter Eleven

The Role of Infections, Lipoproteins and Hyperhomocysteinemia in the Pathogenesis of Vulnerable Atherosclerotic Plaques.

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Abstract

Although cholesterol-lowering drugs have long been the main pharmacological therapy for prevention of cardiovascular disease (CVD), numerous observations contradict the view that elevated low-density lipoprotein cholesterol (LDL-C) is a causative factor in the pathogenesis of atherosclerosis. Inflammation and oxidized LDL (ox-LDL) have been identified as potent risk factors for CVD, but the origin of these factors is unclear. Our concept is that the vulnerable plaque is a micro-abscess created by obstruction of vasa vasorum by aggregates of microbes and lipoproteins, exacerbated by homocysteinylated LDL, endothelial dysfunction and impaired erythrocyte deformability. Obstruction of vasa vasorum by lipoprotein aggregates containing microorganisms leads to ischemia of arterial wall, intramural cell death, rupture of capillaries with haemorrhage, and escape of microorganisms into the intima, leading to inflammation and creation of the vulnerable plaque. This explanation resolves the many observations that contradict the cholesterol hypothesis and implicates inflammation and ox-LDL as secondary phenomena in the origin of atherosclerosis.

Clinical contradictions to the cholesterol hypothesis

Numerous observations are incompatible with the hypothesis that either elevated total blood cholesterol (tC) or elevated low-density lipoprotein cholesterol (LDL-C) is a causal factor in CVD:

1. No study of unselected individuals has shown an association between

tC or LDL-C and the degree of atherosclerosis^{1a}.

2. Almost all studies have shown that elevated tC and/or LDL-C do not predict CVD in women, nor do they predict CVD in elderly people, although the large majority of cardiovascular deaths occur in people older than 65 years of age^{2a}.
3. Low tC and low LDL-C are risk factors for coronary heart disease in Russians³ and in patients with rheumatoid arthritis⁴.
4. No cholesterol-lowering trial has shown exposure-response, namely an association between the degree of cholesterol lowering and the clinical or roentgenological outcome^{2b}.
5. Recent studies have shown that tC and LDL-C are lower than normal in patients with acute myocardial infarction, and in one study, mortality increased when cholesterol was lowered further^{5,6}.
6. A recent systematic review showed that LDL-cholesterol in 68 094 elderly people is not associated with or in most cases inversely associated with mortality.⁹¹

Pathophysiological contradictions to the cholesterol hypothesis

A high level of LDL-C in the blood is said to produce endothelial dysfunction or damage, which allows the migration of LDL-C and monocytes into the arterial wall. According to this view, LDL-C is modified by oxidation, and ox-LDL-C is phagocytized by monocytes or macrophages, a process that converts them to foam cells. These processes are considered as the cause of inflammation in the arterial wall⁷. However, several observations contradict these assumptions:

1. The concept that high LDL-C causes endothelial dysfunction is unlikely because there is no association between the concentration of LDL-C in the blood and the degree of endothelial dysfunction⁸.
2. It is unlikely that endothelial dysfunction leads to influx of LDL-C, because in patients with hyperhomocysteinemia caused by inborn

errors of methionine metabolism no lipids are observed in the arterial wall even though there is pronounced endothelial damage^{9a,10}.

3. If inflammation in the arterial wall were the causative factor in atherogenesis, anti-inflammatory treatment should have beneficial effects. However, almost all trials with anti-inflammatory drugs have resulted in increased cardiovascular mortality¹¹.
4. If the current view of the causative role of LDL-C in atherogenesis were true, both inflammation and the deposits of lipids should occur close to the endothelium, but these changes are found predominately in the adventitia^{12,13,14}.

The role of vasa vasorum

In experiments with rabbits Booth et al¹⁵ produced foam cell formation, deposition of extracellular lipid and smooth muscle cell infiltration into the arterial sub-endothelium without any damage of the endothelium by positioning a hollow silastic collar around the carotid artery. Such changes have also been produced by ligating the vasa vasorum of the femoral artery in minipigs¹⁶. As vasa vasorum are functional end-artries¹⁷, and as similar findings are seen in early human atherosclerosis, these investigators concluded that atherosclerosis might be initiated by occlusion of vasa vasorum.

Therefore, the crucial question concerns which factors are able to occlude the vasa vasorum. Simanionok suggested that occlusion of the vasa vasorum results from impaired erythrocyte deformability^{18a}. Stiffened erythrocytes are less able to traverse smaller capillaries and arterioles, and impaired erythrocyte deformability is observed in diabetes, hypertension, smoking, obesity, lack of physical fitness, psycho-emotional stress, advanced age, peripheral arterial disease, acute myocardial infarction and stroke^{18b}.

Another cause of impaired blood flow may be hyperhomocysteinemia, because a high level of homocysteine in the blood causes endothelial dysfunction and a narrowing of the capillaries and arterioles^{9b,19}.

For many years infectious diseases have been known to be associated with CVD. Today at least 100 published reviews discuss this phenomenon,

but almost all investigators believe infections to be secondary to CVD. We suggest that infectious microbes are primary participants in the pathogenesis of vulnerable plaques^{20a,21a}. According to our hypothesis, complexes composed of microorganisms and lipoproteins, enlarged by homocysteinylated LDL aggregates and autoantibodies against homocysteinylated LDL or oxidized LDL, obstruct blood flow through capillaries and arterioles. This effect may be most pronounced in vasa vasorum of the arteries because of high extracapillary pressure^{20b,21b}. Our hypothesis explains the ischemia and hypoxia of the arterial wall observed within the macrophage-rich center of the atherosclerotic lesions²² and is based on the little known, but well documented role of the lipoproteins in the immune system.

The innate lipoprotein immune system

Previously most authorities considered the serum factor anti-streptolysin-S to be an antibody because of its ability to neutralize streptolysin-S, a streptococcal hemolysin toxin. However, in 1939 Todd et al showed that, contrary to the normal reaction of antibodies, the anti-streptolysin-S titer fell below normal values in patients with rheumatic fever at the peak of the clinical symptoms²³. Subsequently, several research groups demonstrated that antistreptolysin-S is identical with the lipoproteins^{20c}. In animals HDL has the main protective effect against infectious microbes and their toxins, but in humans all lipoproteins are protective^{20d}. Human HDL and LDL are able to bind to and neutralize not only streptolysin-S but also many types of bacteria and viruses and their toxic products^{20e,24}. In agreement with these observations, lipoproteins are found to disappear from the general circulation during infections²⁵. Moreover, low LDL is associated with respiratory and gastrointestinal diseases²⁶, most of which have an infectious origin. Moreover, the increased risk of hospital admission because of an infectious disease is associated with low serum cholesterol²⁷. Furthermore, before 1900 persons with familial hypercholesterolemia lived longer than people without this condition, probably because of the protective effect of LDL against the commonest cause of death at that time, infectious diseases²⁸.

Many studies have shown that the lipoproteins adhere to all kinds of microorganisms, producing aggregation^{29,30}. The size of these aggregates may increase in the presence of hyperhomocysteinemia, because the cyclic anhydride of homocysteine, homocysteine thiolactone, reacts with the free amino groups of apoB protein of LDL, causing aggregation of LDL^{31a,32a}. There is also evidence that homocysteinylation of LDL may alter the antigenic properties of LDL, leading to autoantibody formation^{33,34,35}. Reaction with these autoantibodies may further increase the size of the LDL-microbial aggregates.

The vulnerable plaque is a micro-abscess

Aggregates of homocysteinylated lipoproteins with microorganisms may obstruct blood flow within the vasa vasorum, causing ischemia and hypoxia of the arterial wall^{20f}. This obstruction may lead to intramural cell death, vasa vasorum may rupture causing haemorrhage, and the LDL aggregates with their content of microbial products may enter the arterial wall and cause inflammation. If the immune system is functioning optimally, inflammation and reparatory processes convert the necrotic arterial tissue into a fibrous plaque. If the immune system is sub-optimal, the necrotic arterial wall containing lipoprotein aggregates and micro-organisms may rupture into the intima, creating a micro-abscess, the vulnerable plaque. It has been shown that almost all arterial thrombi are associated with vulnerable plaques. Some thrombi are precipitated by rupture of a vulnerable plaque³⁶, but in other cases the thrombus is located adjacent to a superficial erosion of a proteoglycan-rich plaque without rupture³⁷.

In agreement with the conclusion that the vulnerable plaque is a micro-abscess, its temperature is higher than that of the surrounding tissue³⁸. Furthermore, fragments from more than 50 different bacterial and virus species^{39,40,41,42} and even live bacteria^{43,44,45,46} have been demonstrated in atherosclerotic arteries, but not a single one was found in normal arterial tissue. The concept that vulnerable plaques are loaded with microorganisms is also supported by the finding that about 20 % of patients with acute myocardial infarction complicated by cardiogenic shock have bacteraemia and sepsis⁴⁷.

Our concept is that the atherosclerotic, calcified plaques are the healed scars resulting from infections within the arterial wall. We agree with the American pathologist Hans Kaunits, who in a review published almost 40 years ago concluded: “It may perhaps be profitable to pay more attention to speculations that the initiating factor is an infectious agent....In a wide variety of pathological conditions, cholesterol forms a large part of the lesion. This is true in scars, tubercles, gummata, old fibroids, thrombi, cholesteatomata, where it forms a complicated tissue in combination with calcium, fibrin, collagen, and other substances”⁴⁸.

Foam cells and atherogenesis

The presence of foam cells is a frequent finding in atherosclerotic arteries. According to the currently prevailing hypothesis, foam cells are created by macrophages which phagocytize oxidized cholesterol by interaction with the scavenger receptor. However, in vitro experiments have shown that lipopolysaccharides (LPS) from several of the pathogens which are most frequently reported in human atheromas are able to convert macrophages to foam cells in the presence of human LDL^{49,50,51}.

Macrophages phagocytize lipoprotein aggregates by phagocytosis and destroy the microorganisms by oxidation with reactive oxygen radicals⁵². It is therefore much more likely that the presence of oxidized cholesterol in the artery wall and in the circulation is the result of a normal oxidative process of the innate immune defence system. Therefore, our conclusion is that cholesterol is not oxidized in the interstitium but is oxidized inside the macrophages together with the microorganisms and their toxic products.

Intimal fatty streaks of the aorta and peripheral arteries are composed of aggregated foam cells located close to the arterial endothelium. Probably these foam cells are destined to enter the circulation, and their presence is a normal phenomenon in healthy people. This is the only credible explanation, since aortic and arterial fatty streaks are present even in the fetus and in early childhood^{53,54}, presumably reflecting a normal and reversible response to infections.

Evidence for infections as a causative factor in atherosclerosis and

CVD

Numerous observations and experiments suggest that infections are not secondary to CVD but are primary factors in the pathogenesis^{55,56}. For instance, influenza epidemics are associated with an increase of CVD mortality^{57,58}. About a third of patients with acute myocardial infarction or stroke have had an infection during the preceding month⁵⁹. Bacteraemia^{60,61}, HIV^{62,63}, serological markers of infection^{64,65} and periodontal infections^{66,67} are risk factors for CVD. Furthermore, infected children who die from an infectious disease have narrowing of the coronary arteries⁶⁸, and those who survive have thickening of the carotid intima-media⁶⁹.

Animal experiments support microorganisms as pathogenic factors in atherosclerosis

The strongest argument for causality is experimental creation of atherosclerosis by the suspected factor, and several such experiments with infectious microorganisms have been successful. Atherosclerosis has been produced or accelerated in chickens by infection with Marek's disease herpesvirus⁷⁰ and in mice by infection with *Chlamydia pneumoniae*, *Mycoplasma pneumonia* and *Porphyromonas gingivalis*^{71,72}. Evidence of early atherosclerosis has also been produced both in normocholesterolemic and in hypercholesterolemic minipigs by infection with *Chlamydia pneumoniae*, alone or together with influenza virus⁷³. In accordance with our hypothesis vascular damage and endothelial dysfunction in this experiment were most prominent in the co-infected pigs and less pronounced in the hypercholesterolemic pigs.

Prevention and treatment of atherosclerosis

According to our concept of the pathogenesis of atherosclerosis, the war against CVD should concentrate on counteracting infectious diseases, improving immune function, and eliminating factors that obstruct the blood flow within the vasa vasorum.

For many years treatment with cholesterol-lowering statin drugs has been

the standard therapy for prevention of CVD. As the lipoproteins protect against infections, it may seem contradictory that cholesterol lowering with statin drugs is protective against CVD. However, no statin trial has shown an association between the degree of cholesterol lowering and outcome^{1b}, and the beneficial effect of statin drugs must therefore depend on other effects. It is likely that statin treatment would be more beneficial if it did not lower cholesterol.

Many authors claim that statin treatment lowers the risk of infectious diseases. However, in these studies the investigators have compared statin-treated patients with non-treated control individuals from the general population. These studies contain a serious bias because of the fact that low cholesterol levels predispose to infectious diseases. Most statin-treated patients have lived most of their lives with high cholesterol levels, whereas many of the untreated controls may have lived their lives with low cholesterol levels. Furthermore, many patients discontinue statin therapy because of unacceptable side effects. It is therefore impossible to know, whether the better outcome of the statin treated patients is caused by their high cholesterol, or by statin treatment. The lack of anti-infectious efficacy of statin therapy has been documented in various ways. For instance, Becker et al have shown that statin treatment of stroke patients increases their risk of infection⁷⁴. In a study of patients with fever by de Saint Martin et al., a significantly larger number of those who were on statin treatment was admitted to intensive care units, compared with non-users ($p=0.009$)⁷⁵.

Prevention of cardiovascular disease by antibiotics has been largely unsuccessful, apparently contradicting our hypothesis. However, in most of these trials patients have received a single antibiotic, and most of them have been of relatively short duration⁷⁶. Since a large number of different microorganisms has been identified in atherosclerotic arteries, use of a single antibiotic is unlikely to be beneficial. Moreover, viral agents, such as *Herpesvirus* or *Cytomegalovirus*, which have also been implicated in atherogenesis, are generally resistant to antibiotics.

In a trial by Paakkanen et al. of 144 patients with acute coronary syndromes, the participants were randomly divided to receive a three-month treatment of clarithromycin or placebo and were followed for an average of 404 days (138-924 days). The outcome of this trial documented a decrease

in major adverse coronary and cerebrovascular events (19 % vs 40 % events), and the benefit was most pronounced among those with complement component C4B deficiencies⁷⁷.

Antibiotics may be useful in treatment of acute myocardial infarction. As bacteraemia and sepsis are common findings in life-threatening cases, we suggest that a blood culture should be obtained in patients with acute coronary syndrome. If the blood culture is positive, we anticipate that the course of the disease may be improved with an appropriate antibiotic.

Vaccination may also be useful. In a meta-analysis of 11 cohort studies Vlachopoulos et al found that pneumococcal vaccination was associated with a decreased risk of cardiovascular events and mortality in elderly people, in particular among those with high cardiovascular risk⁷⁸. Furthermore, several observational and case-control studies⁷⁹ and two randomized trials^{80,81} have shown that influenza vaccination protects against CVD.

Periodontal disease is a risk factor for CVD, and Piconi et al. have documented that treatment of patients with periodontal disease had a better angiographic outcome than observed in any statin trial⁸². Furthermore, according to a nationwide population study, tooth scaling is associated with a decreased risk for future cardiovascular events⁸³.

Infectious diseases are associated with dyslipidemia, reflecting a metabolic response to infections^{84,85}. Thus the dyslipidemia associated with atherosclerosis may be attributed to the metabolic response to infection. Young adults with dyslipidemia are associated with an increased coronary artery calcium score later in life⁸⁶. A probable interpretation of this observation is that increased arterial calcification is attributable to healed and calcified atherosclerotic plaques as a result of spontaneously resolved infections. Consequently, prevention and treatment of atherosclerosis is more likely to be accomplished by prevention and elimination of infections than treatment of dyslipidemia, a secondary metabolic response to infections⁸⁷.

An apparent contradiction to our hypothesis is that a lowering of blood homocysteine levels by high dose folate, pyridoxal, and cobalamin has generally been ineffective in preventing adverse vascular events⁸⁸. However, the assay for plasma homocysteine determines the quantity of

homocysteine bound to plasma proteins by disulphide bonds, but neither homocystine disulphide nor protein-bound homocysteine has been reported to react with the amino groups of LDL to cause aggregation^{31b}. This effect is only created by homocysteine thiolactone^{32b}. Although several of the B vitamin secondary prevention trials significantly lowered plasma homocysteine levels⁸⁹, none of these trials utilized an assay for plasma homocysteine thiolactone, the only molecular species of homocysteine which causes LDL aggregation^{31c,32c}. Future trials are needed to study the effect of B vitamin intervention and other homocysteine-lowering protocols on prevention of vascular disease by utilizing an assay for plasma homocysteine thiolactone⁹⁰, the reactive molecular form of homocysteine that causes aggregation of LDL, leading to obstruction of vasa vasorum and creation of vulnerable plaques^{20g}.

Summary

Our concept is that microbial infection, hyperhomocysteinemia, aggregated lipoproteins, and endothelial dysfunction are major factors in the pathogenesis of atherosclerosis. That elevated LDL-C is the main cause of CVD dominates the view of the worldwide scientific community, although hundreds of observational and experimental studies fail to satisfy most of Bradford Hill's criteria for causality. A major problem is that almost all investigators and medical journals in this field are economically dependent on the drug companies. In recent years there has been increased scepticism among medical scientists concerning the supposed benefits from statin treatment. Our hypothesis may hopefully increase the interest of the medical profession in more effective methods of prevention and treatment of CVD.

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Chapter Twelve

Cardiovascular Disease is Primarily Due to Blood Clotting^{*}

Malcolm Kendrick, MD

Abstract

This chapter proposes that atherosclerotic plaques, the underlying cause of cardiovascular disease (heart attacks and strokes) are caused by two main processes. First, damage to the lining of larger arteries (the endothelium), followed by blood clotting. These clots are then incorporated into the arterial wall where, if the damage is rapidly repeated, or the blood clots formed are larger/more difficult to break down, the clot will turn into an atherosclerotic plaque. Therefore, factors that can damage the endothelium e.g. smoking, stress, high blood sugar levels, areas of turbulent flow will increase the risk of CVD. In addition, pro-coagulant factors will increase the risk of CVD e.g. air pollution, high fibrinogen levels, heat, cold, type II diabetes, stress, steroid use.

This hypothesis explains why plaques never form in veins, or in pulmonary blood vessels – where endothelial cells are under far less biomechanical strain. It also explains how statins reduce CVD risk. Statins increase nitric oxide synthesis, which protects the endothelium, and is the single most potent anticoagulant agent in nature. This hypothesis also explains how LDL can (in some situations increase CVD risk), as LDL stimulates platelet aggregation (the first step in clot formation). On the other hand, HDL has potent anti-coagulant properties. This 'clotting' hypothesis of CVD can be used to explain all of the factors known to cause, or protect against, CVD.

Introduction

Over one hundred and sixty years ago Karl von Rokitansky studied the

narrowings and thickenings found in human arteries (atherosclerotic plaques) and decided that they looked almost exactly like blood clots. He therefore proposed that they were, in fact, blood clots – in various different stages of ‘repair’.

His scientific rival, Rudolf Virchow, studying the same phenomenon, had noted that these plaques contained a high percentage of cholesterol. Based on this single observation, he conjectured that this cholesterol must have been absorbed into the artery walls, from the bloodstream, creating further inflammation and thickenings.

This was the first time that the ‘cholesterol hypothesis’ had been proposed. Unfortunately, Virchow won the scientific argument with Rokitansky, at which point the cholesterol hypothesis became the bed rock of all future thinking about cardiovascular disease. Even if most researchers have no idea where the original idea came from.

Had Rokitansky won the debate, the direction of research into heart disease would, I believe, have gone in the correct direction. We would have realized that LDL/cholesterol has a very minor and relatively unimportant role in creating atherosclerotic plaques; a role that relates to the downstream function of lipoproteins within blood clotting. We would long ago have fully understood the underlying mechanism of cardiovascular disease, and our management of it would be far in advance of where it is today.

In this Chapter I will lay out the ‘blood clotting’ hypothesis in as concise a form as possible. I will look at the process itself, and then establish how it fits with the various risk factors for cardiovascular disease that have been identified. For the sake of simplicity, I will call this hypothesis the ‘*atherothrombotic hypothesis*’, although this term has been used before to describe related phenomena, and is not fully accurate in this case.

The complexity of the atherothrombotic process

Before starting, I should state that much of what is described here should be defined as normal and healthy. For example, damage to the innermost layer of the artery, the endothelium, leads to blood clotting. Indeed, the process of clot formation (thrombosis) is a completely healthy physiological phenomenon. It protects us from death each and every day. Without the ability of blood to clot, the smallest scratch could be fatal. One small cut

and we would just slowly bleed to death. People with haemophilia, for example, have serious health problems due to bleeding heavily into joints and suchlike.

On the other hand, if we clot too readily, if we are in a 'hypercoagulable' state, this too is far from healthy. People with an increased propensity of blood clotting are far more likely to die from strokes and heart attacks and pulmonary emboli and suchlike. It does not take much, one way or another for the blood clotting system to go wrong. So we are not talking about black and white, on or off, we are looking at a dynamic system that can tip one way or another – causing problems in either direction.

For example, there are two forms of stroke. Haemorrhagic and ischaemic. A haemorrhagic stroke occurs when a blood vessel in the brain bursts and blood enters the brain tissue, destroying parts of it. An ischaemic stroke occurs when a blood clot blocks an artery in the brain, stopping blood flow, preventing oxygenation and causing brain tissue to die.

These are clinically indistinguishable, unless you do a brain scan. One type of stroke is caused by excess bleeding, the other caused by a blood clot. If you try to treat a haemorrhagic stroke with an anti-coagulant, the patient will most likely die. If you try to treat an ischaemic stroke with an anti-coagulant the patient will most likely live.

In addition, it would be true to say that the coagulation system has more feedback loops and complexity than any other in the body. For every ten factors that are trying to get the blood to clot, there are another ten trying to ensure that it does not, or that the clotting process is stopped in its tracks. All is a constant balance, a highly dynamic system – some might say perhaps even chaotic.

It does not take too much to flip the system one way or another. The analogy of a butterfly fluttering its wings in the rain forest and causing a hurricane half way around the world could be appropriate, in that apparently very small and insignificant changes in one part of the clotting system can lead to a major breakdown elsewhere. Often in ways that can seem counter-intuitive.

The idea of chaos theory is further appropriate here in that agents that may appear almost exactly the same can create very different effects. Some anticoagulant drugs decrease the risk of heart disease, whilst others have no effect on the risk of heart disease, or may even increase the risk. Other

anticoagulants can decrease the risk of stroke, without affecting heart disease. Simple, it is not.

At the risk of bringing in too much jargon too early, there are also long-term abnormalities e.g. antiphospholipid syndrome, Factor V Leiden and raised Lp(a). These lead to an increased tendency to blood clotting, and an increased risk of cardiovascular disease. In addition, there are temporary factors at work, that that make the blood hypercoagulable (more likely to clot) e.g. stress, smoking, use of steroids, dehydration, hyper/hypothermia and infections. All of these raise CVD risk, but sometimes for only a period of days, hours, or even minutes.

So, when you are looking at blood clotting and blood clotting abnormalities it is difficult to be absolute. A causes B, X leads to Y. But A may only cause B, so long as D and E are present and not Q and V. However, the general theme here is straightforward. Factors that stimulate, or accelerate blood clotting, or interfere with the correct repair of blood clots, will generally increase the risk of cardiovascular disease CVD.

What are the players in the game?

The endothelium

The endothelium is the single layer of cells that lines all blood vessels. These cells are flat, and thin, and join together at their boundaries with no gaps between. A bit like floor tiles, perhaps, although far more flexible and most certainly far more biological active. An important point to note here is that endothelial cells act as a barrier to anything in the blood stream leaking into the wall of the artery itself.

However, having just said this, as blood vessels become smaller and narrower, the endothelial cells develop holes in them known as fenestrations. This does allow various substances to leak out of the blood into the tissues and organs underneath. Were this not the case, few nutrients could get out of the blood, which would somewhat defeat the point of blood circulation.

For the purposes of this discussion we are not interested in the fenestrated form of endothelium lining smaller blood vessels, arterioles, venules and the like, because of the significantly different structure that is

present. This form of endothelium does not act as a barrier and, more critically, it does not lie over tissues that contain powerful blood clotting activators. In short, we are looking at the congruent endothelium lining the larger blood vessels.

Whilst it is known that endothelial cells have a vast array different functions, I am restricting myself to looking at three. The first of which is that they produce nitric oxide (NO). Nitric oxide has two major functions. It is the most powerful anti-coagulant agent in the body. It also stimulates the smooth muscle within larger blood vessels to relax. This opens these arteries up, allowing increased blood flow.

This is why most agents used to treat angina are nitrates. The first of them to be identified was glyceryl trinitrate (GTN). The benefits of GTN was first noted by those working in dynamite factories, where men stirring the nitro-glycerin mixture found that their angina disappeared as they did so. Nitro-glycerin was turned into GTN tablets, and renamed. GTN is still used to stop angina attacks which occur when the blood vessels supplying the heart narrow, reducing oxygen supply, and causing heart muscle pain. GTN opens up the arteries, improves blood supply, and stops the pain.

If endothelial cells are ‘stressed’ or damaged, they produce far less NO. This has two important effects. First, the level of ‘anticoagulant’ falls, and the blood vessels constrict, raising pressure and turbulent flow over the endothelium. This makes it far more likely that clots will form.

Another important function of endothelial cells, is that they prevent contact between the blood and the inner arterial wall. This is critical because, lying within the arterial wall, is a high concentration of tissue factor (TF). This is the most powerful single clotting factor that exists. It triggers the ‘extrinsic’ clotting cascade and, essentially, overpowers all feedback systems, until the damage and tissue factor are both covered over.

Clearly this makes sense. If an arterial wall is damaged through trauma, the blood needs to clot very quickly, and directly on the site of the damage, to plug the hole. Therefore, this is where the primary agent for blood clotting lies. Which means that if endothelial cells are damaged, or stripped off, a thrombus will form very quickly over the area of the damage – triggered by tissue factor.

At which point a final essential characteristic of endothelial cells comes into play. Something that requires a bit more explanation, via a slight

detour. If we look at skin cells, which grow upwards from the stratum basale, they gradually become thinner, before turning into the stratum corneum (outer surface of the skin). They then flake off and are replaced from underneath.

However, endothelial cells do not move upwards from within the arterial wall. There is no underlying stratum of endothelial cells that grow towards the surface. So, where do the replacement cells come from? The answer is that they are produced in the bone marrow in the form of endothelial progenitor cells (EPCs), which then circulate in the bloodstream.

Which means that if endothelial cells die (for whatever reason) or are stripped off, they are replaced by EPCs from above – if that is the correct way to think of it. EPCs, when they detect an area of endothelial damage, (inevitably already covered by a thrombus), stick to it, mature and form a new layer of endothelium on top of the thrombus.

In this way something very significant just happened. The thrombus now lies underneath the endothelial layer (within the artery wall itself). This actually answers the question from Virchow that Rokitansky could not answer. Namely, how can a blood clot form within the artery wall? Answer, it cannot, the blood clot is created on an area of damaged, or missing endothelial cells, then the endothelium re-grows on top of it.

Once again, from a physiological perspective, this makes perfect sense. If you damage your skin it will bleed, then a clot will form over the area of damage. The skin will then re-grow under the hardened clot (scab), once the skin has repaired underneath, the scab will simply fall off. However, if this happened in an artery wall, the clot/scab that fell off would travel down the artery until it narrows. At which point it would jam, potentially blocking the artery completely. If the thrombus/scab travelled into the brain it would cause a stroke, potentially fatal. So thrombi that form over areas of arterial damage must be resorbed into the artery wall itself.

A final point to mention here is that EPCs do not necessarily become mature endothelial cells. They can also go down another developmental pathway to become monocytes (a form of white blood cell involved in the immune system). These monocytes can further mature into macrophages. Another white blood cell type. Macrophages attack bacteria and viruses and also any other ‘alien’ tissue that they find.

Macrophages are the ‘clear up’ cells of the immune system. Interestingly.

in order to clear up the waste, macrophages first use NO to ‘oxidize’ the alien material. This oxidized material is then engulfed by the macrophage which transports it to lymph glands where it is broken down and, eventually, removed from the body.

In summary, the endothelium is a critical player in the health of the cardiovascular system, primarily through NO synthesis. When healthy, the endothelium is also protective against blood coagulation, by separating the blood from the TF found in the deeper arterial wall. If clots do form, EPCs play a further critical role in covering up the clot, and then clearing up the ‘damage’ by transforming themselves into blood cells. Yes, it is all very clever.

The clotting/coagulation system

This is, as previously mentioned, an enormously complicated system with many, many, different players involved, along with many feedback systems. At the risk of oversimplifying, for the purposes of this discussion we can divide the coagulation system into the extrinsic clotting system and the intrinsic clotting system.

When we are talking about CVD it is primarily the extrinsic clotting system that is more important than the intrinsic clotting system. In general, significant clots will not form without activation of the extrinsic system. [Of course, it is completely artificial to try to separate these systems in this way, as they share many of the clotting factors and overlap all over the place. But for the sake of simplicity I shall talk about intrinsic and extrinsic as though they were different processes].

As with everything, however, there are exceptions to this rule i.e. situations where you have a healthy and intact endothelium and major clots can still form due to activation of the intrinsic clotting system. There are two main clinical situations where this happens:

- Deep vein thrombosis (DVT)
- Atrial fibrillation causing clots to form within the heart

If a patient lies immobile in a bed, in a plaster cast, there is a high risk

that the blood can become virtually stationary within a vein. At which point the intrinsic clotting system can activate. This will start a blood clot forming within a vein (blood flow is too rapid and turbulent for this ever to happen in an artery). This is the basic mechanism behind a DVT.

Such clots are relatively weakly stuck together, in comparison to clots formed by the extrinsic pathway. Which means that a section of them, or the whole thing, can break off and travel up into the heart, then travel through the heart into the lungs where it can get stuck as the blood vessels narrow. This causes a pulmonary embolism (PE), which can often be fatal. [If the clot gets stuck in the heart this is inevitably fatal].

The way to protect against this is to use an anticoagulant that blocks some of the clotting factors of the intrinsic clotting system. The most common of these drugs would be warfarin, another would be low molecular weight heparin (LMWH). Many patients in hospital who are bed bound, for one reason or another, are given LMWH as prophylaxis against DVT and PE, until they get back on their feet. You cannot give heparin long term as toxicity builds up.

Warfarin has another major use, in Atrial Fibrillation. Atrial Fibrillation (AF) is a condition whereby the atria (upper chambers in the heart) do not contract in a regular fashion, instead they ‘fibrillate’, whereby they twitch very fast and in an irregular rhythm. When the atria fibrillate (for whatever reason), small blood clots can form within the chambers of the atria themselves. These can break free, then travel out of the heart and into the rest of the body, where they will get stuck. Most commonly, these clots travel up into the brain where they cause strokes. Thus, people with AF are given warfarin to prevent strokes.

This treatment is highly effective. However, although warfarin, LMWH and other new oral anticoagulation agents (NOACs) can prevent DVTs, PE, and one specific form of stroke, they have little benefit on atherosclerotic plaque formation, or death from heart disease/CHD. In fact, some studies have shown that warfarin can accelerate plaque development – whilst reducing the risk of MIs (slightly):

‘The present study demonstrates that VKA (warfarin) treatment is associated with accelerated calcification of atherosclerotic plaques in humans.’
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3430691/>

But there may be other things going on here as well. I only include this fact to emphasize that we are looking at highly complex systems, where the apparently obvious answer is unlikely to be correct. As H.L. Mencken famously said *‘For every complex problem there is an answer that is clear, simple, and wrong.’*

In summary, although the intrinsic clotting system – which is mainly responsible for DVT, PE and a specific type of strokes in AF - is an important cause of death from certain forms of, what can be called, cardiovascular disease. It does not have much of a part to play in CVD due to plaque growth and development.

To understand heart attacks and ischaemic strokes we need to look more closely at clots created by the extrinsic system. This system, as mentioned before, is primarily triggered by injury to the endothelium. Perhaps the most concise description of how this works is from Wikipedia

*‘Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining the vessel. Exposure of blood to the space under the endothelium initiates two processes: changes in **platelets**, and the exposure of subendothelial **tissue factor** to plasma Factor VII, which ultimately leads to fibrin formation. Platelets immediately form a plug at the site of injury; this is called primary hemostasis. Secondary hemostasis occurs simultaneously: Additional coagulation factors or clotting factors beyond Factor VII respond in a complex cascade to form fibrin strands, which strengthen the platelet plug.’* <https://en.wikipedia.org/wiki/Coagulation>

The main players in the initial thrombus formation are platelets (small ‘sticky’ cells that clump together to form a plug). After platelets have clumped together, fibrinogen acts to bind the thrombus together. Fibrinogen is a small strand of protein which, when many of them are stuck together, end-to-end, form fibrin. Fibrin is a bit like fishing line. Long, thin, and very strong. It tangles itself around the developing thrombus, binding it together very strongly.

However, at this point it should be emphasized that thrombus contain almost every substance found in the bloodstream. They are not just made up of platelets and fibrin. Once a thrombus gets going everything is either dragged in, or plays a part in thrombus development: platelets, clotting factors, thrombin, white blood cells, red blood cells, lipoproteins, including LDL-C (aka ‘bad’ cholesterol). Indeed, if you choose to investigate it, you find connections between almost everything found in blood, and the process

of coagulation. For example, platelets and LDL-C.

'Platelets and lipoproteins are intimately involved in the pathogenesis of a wide variety of disease including atherosclerosis, thrombosis, and coronary heart disease. Evidence accumulated over the years suggests the possibility of a direct relationship between plasma lipoproteins and the hemostatic function of platelets. A number of studies demonstrated that native LDL enhanced the platelet sensitivity to stimulation and induced platelet activation.' Yashika Gupta, V. Mallika* and D.K. Srivastava: *'INTERACTION OF LDL AND PLATELETS IN ISCHAEMIC AND ISCHAEMIC RISK SUBJECTS'* Indian Journal of Clinical Biochemistry, 2005, 20 (1) 97 – 92

In short LDL-C (which is what we call 'bad' cholesterol, in another confusing and scientifically illiterate fashion) makes platelets more 'sticky' and thus thrombi more likely to form. So, here we can see a possible connection between LDL and increased risk of coagulation and thus, of course, CVD.

The enormous complexity of the clotting system is further revealed when we look at High Density Lipoproteins (HDL) a.k.a. 'good' cholesterol. It is widely accepted that HDL is protective against death from CVD. It is generally believed that this protection comes through the process of reverse cholesterol transport i.e. HDL sucks cholesterol out of plaques. [Which I do not believe]

However, this is probably not how HDL works. It has other important and potent effects on blood coagulation:

'Furthermore, HDL stimulates the endothelial production of nitric oxide and prostacyclin, which are potent inhibitors of platelet activation. Thus, HDL's antithrombotic actions are multiple and therefore, raising HDL may be an important therapeutic strategy to reduce the risk of arterial and venous thrombosis.' <http://www.ncbi.nlm.nih.gov/pubmed/24891399>

Even red blood cells (RBCs) get in on the act. They appear to have little active role to play in the initial stages of blood clotting, but when a clot gets going RBCs are dragged in and once this has happened they have a hugely important role in helping the clot to contract and stabilize. They aggregate within the 'core' of a clot, change their structure to polyhedrons and, essentially, work alongside fibrin to prevent the clot breaking apart. http://www.uphs.upenn.edu/news/News_Releases/2014/01/weisel/

RBCs have more recently been found to be a critical component of atherosclerotic plaques where they also seem to have an important role in

accelerating plaque formation:

'In summary, potentially the erythrocyte (Red Blood Cell) is a new player in atheromatous lesion formation. The red cell membrane hides constituents that are lipid rich, can bind to macrophage scavenger receptors, and are associated with risk factors for atherosclerotic disease. The hypothesis that red cell membranes contribute to atheroma formation in coronary arteries is challenging.'
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1767211/>

In fact, red blood cell membranes are, possibly, the only structure in the human body that can become cholesterol crystals (so much cholesterol do they contain). When Virchow saw cholesterol in plaques what he was looking at, almost certainly, was cholesterol crystals. These have little to do with LDL-C, or any other form of lipoprotein. Their genesis is from RBC membranes.

'The view that apoptotic macrophages (dead macrophages) are the predominant source of cholesterol in progressive (atherosclerotic) lesions is being challenged as new lines of evidence suggest erythrocyte membranes contribute to a significant amount of free cholesterol in plaques.'
https://www.researchgate.net/publication/5958670_Free_cholesterol_in_atherosclerotic_plaques_Where_does_it_come_from

Hopefully, at this point, things have not become too unstructured, or confusing. I wished to give the sense of the immense complexity of the systems operating here. Heart disease, or ischaemic heart disease or cardiovascular disease is not, and never was, the case of finding a few 'risk factors' that could explain everything. It is a dynamic and interconnected process. You cannot understand it, bit by bit, in a reductionist fashion. Knowing how each 'factor' works, tells you little about the entire system. It is like trying to describe a football match by accurately describing the pitch and the individual players, without watching the match.

At this point, before attempting to pull everything back into a coherent structure, I will provide one more example of how almost impossibly clever human clotting physiology is, and how many actors there are.

Lp(a)

Lp(a) is the shortened version of Lipoprotein (a). It has long been recognised in certain populations to have a role in increasing the risk of

heart disease. Lp(a) is a form of lipoprotein. Interestingly it has exactly the same structure as LDL. The thing that we try to lower with statins and suchlike. Lp(a) could more accurately be called LDL(a). For that is what it actually is.

The only difference between LDL and Lp(a) is that Lp(a) has a different, and complex protein, attached to it, called apolipoprotein (a). This interesting thing about this protein is that it has exactly the same chemical structure as plasminogen. Plasminogen, not mentioned before, is an enzyme. It becomes incorporated into clots as they form. If it is activated, it cuts apart the strands of fibrin and helps to break the clot apart. Plasminogen, in turn, is activated by Tissue Plasminogen Activator (tPA). tPA can be made artificially and is one of the original 'clotbusters' used in the acute treatment of strokes and heart attacks.

However, apolipoprotein (a) cannot be activated by tPA, because it is folded in a different fashion to plasminogen, which means that tPA simply bounces off. Thus thrombi containing a lot of Lp(a) are highly resistant to being broken down.

Why would the body produce such a thing? What could possibly be its purpose? The answer is that Lp(a) is found in animals that cannot synthesize vitamin C such as: great apes, fruit bats, hedgehogs and, of course, humans. Animals that cannot produce vitamin C are at risk of scurvy. The primary problem in scurvy is that connective tissue cannot be properly formed. Connective tissue supports small blood vessels (capillaries) and so they start to bleed profusely.

When this happens Lp(a), to put its action into its simplest fashion, acts as glue to plug the cracks in the capillaries and stop the bleeding. Thus, Lp(a) protects against some of the most serious effects of scurvy, because a clot that contains a lot of Lp(a) is completely resistant to plasminogen. Thus, once formed, such clots are very difficult to remove.

Of course collagen, and other connective tissue is also present in larger arteries and veins, so cracks can also develop here. Based on this knowledge, a researcher called Matthias Rath made the conjecture that vitamin C supplementation could protect against CVD by ensuring that the blood vessels were kept healthy, and did not have any cracks. No cracks, no activation of Lp(a) and thus far fewer clots forming.

Rath convinced Linus Pauling (the double Nobel prize winner) that this

hypothesis was correct and Pauling spent the later years of his life promoting Vitamin C as a cure for heart disease and strokes – and many other things. For which he was widely ridiculed by the medical establishment.

The most interesting fact here is that having a high Lp(a) will not be a risk factor for heart disease in those with healthy endothelial cells and good supportive collagen – and other connective tissue. However, once the endothelium comes under attack (for whatever reason) a high Lp(a) level may well accelerate plaque formation. Which may explain why Lp(a) is a risk factor in some populations, and not others.

Plaques are clots

Whilst I have talked quite a lot about clotting and the endothelium and suchlike I have not yet outlined the overall process of atherosclerotic plaque development and growth. The underlying atherothrombosis hypothesis is that plaques are, simply, blood clots in various stages of repair (as outlined by Rokitansky).

This hypothesis is strongly supported by looking more closely at the structure of plaques. Here are two extracts from a paper in the *American Heart Journal* called: '*A Definition of Advanced Types of Atherosclerotic Lesions and a Histological Classification of Atherosclerosis.*'

'The architecture of some multilayered fibroatheromas could also be explained by repeated disruptions of the lesion surface, hematomas, and thrombotic deposits. Organization (fibrosis) of hematomas and thrombi could be followed by renewed accumulation of macrophage foam cells and extracellular lipid between the newly formed fibrotic layer and the endothelial surface...

...The fissures and hematomas that underlie thrombotic deposits in many cases may recur, and small thrombi may reform many times. Repeated incorporation of small recurrent hematomas and thrombi into a lesion over months or years contributes to gradual narrowing of the arterial lumen. Some thrombi continue to enlarge and occlude the lumen of a medium-sized artery within hours or days.' <http://circ.ahajournals.org/content/92/5/1355.full>

Simplifying the language here, what the *American Heart Journal* paper is saying is that a significant number of plaques effectively have the appearance of tree rings. With layer upon layer building up, one on top of the other. The only possible explanation for such a structure is for blood

clots to have formed repeatedly, over the same spot. Of course, not all plaques look like this. I would conjecture that, attack by macrophages and other healing processes, turns many plaques into an amorphous mass with no particular structure. So the evidence of repeated thrombus formation is lost.

Another important point that I want to bring in here is covered by the last part of the second quote: '*Some thrombi continue to enlarge and occlude the lumen of a medium-sized artery within hours or days.*' What this is saying is that the final event in coronary artery disease, the complete blockage of a coronary artery, represents exactly the same process as caused the atherosclerotic plaque to develop and grow in the first place. Namely, thrombus forming over an area of artery wall damage. The final event is the same as all the other events.

Currently with the lipid, or cholesterol hypothesis we require two, essentially, unrelated physiological processes to take place. First LDL-C is absorbed into the artery wall causing inflammation, plaque development and growth. Once the plaque has reached a certain size, or becomes 'vulnerable' it can rupture leading to the final event. A large blood clot forming over the plaque, blocking an artery and causing a heart attack. Or (if the clot forms in the arteries in the neck – carotid arteries), breaking off and travelling into the brain where it causes a stroke.

Two different processes with two sets of different causal 'factors?' Of course this might be true, but if we are looking at one disease, atherosclerotic plaque development, growth and final blockage, it is much more likely that it is actually caused by a single process, rather than two.

Returning to the actual process of plaque development and growth. The first step in the process is that endothelial cells become damaged, die, or are simply stripped off. At which point a blood clot forms over the area, stimulated primarily by the exposure of the blood to TF. Once the clot has stopped growing it is covered by EPCs, which form a new layer of endothelium over the top of the clot. The clot now lies within the artery wall where it is attacked by monocytes and macrophages. This breaks it down, and clear it away. This is normal, and healthy, and is probably happening all the time in most people.

However, problems start where this sequence happens at an increased frequency, over the same area. At which point, the repair processes become

overwhelmed, and the plaque effectively starts to grow within the artery wall. When this starts to happen macrophages, working away to clear up the damage, become overwhelmed by the detritus, bloat up into foam cells – and can no longer function. Many of them then die, releasing the gunk of half-digested lipoproteins, red blood cell membranes, Lp(a), fibrin strands back into the plaque. This gunk is often referred to as the ‘lipid core’, although it contains far, far, more than lipid.

Adding to the problem, the endothelium lying on top of plaque tends to be less healthy than normal endothelium, it produces less NO etc. Which adds to the likelihood of repeated thrombus formation at the same point, although, until it reaches a significant size, it does not actually cause any narrowing of the artery. Under normal blood pressure the plaque is pushed outwards, causing a swelling of the artery wall, but no narrowing of the lumen.

The end game in this process is when the thin fibrous cap overlying the plaque ruptures, exposing the contents to the bloodstream. The contents are all highly thrombogenic, stimulating rapid blood clot formation which can fully block the artery. This causes a myocardial infarction, or heart attack.

Alternatively, plaque rupture leads to a clot forming on top of an atherosclerotic plaque in an artery in the neck. This will then break off and travel the brain where it gets stuck, causing an ischaemic stroke. And that is pretty much the atherothrombotic hypothesis.

Arteries and veins

Perhaps the strongest single piece of evidence in support of this hypothesis is that atherosclerotic plaques never form in veins (although there are a couple of exceptions to this, which I will explain later). Veins and arteries are bathed by exactly the same substances in the blood. The LDL-C level is exactly the same, for example, so why does not LDL-C become absorbed into vein walls, leading to plaques?

Arteries and veins also have exactly the same basic structure. Endothelium lies over smooth muscle with a deeper layer of connective tissue (the adventitia) beneath. Veins are thinner than arteries, as they have to deal with a much lower blood pressure, but otherwise they are identical. So why, in an otherwise healthy person, do plaques never, ever, develop in

veins, or in any blood vessels in the lungs (veins or arteries). A fact that cannot be explained by the cholesterol hypothesis.

The answer is, of course, simple. Veins are exposed to far less biomechanical stress. The pressure in veins is far lower, the blood flow is less turbulent, and so the endothelium is far less ‘stressed.’ Indeed, the main areas where plaques develop in arteries, are at bifurcations (where one artery splits off another one) and in the heart, where the coronary arteries are exposed to the compression of the heart, every second of every minute and every hour of every day.

In short, in places where blood pressure is high, flow is turbulent, and the artery is under constant physical stress, the endothelium is far more likely to die, or be stripped off, and clots are far more likely to form. This level of endothelial ‘stress’ is not present in veins, so clots don’t start here in the first place. Atherosclerotic plaques do not develop in the lungs either, where the blood pressure is far lower than in the arteries in the rest of the body. As with everything, there are exceptions to these rules:

- When veins are used in coronary artery bypass grafts
- When there is higher than normal blood pressure in the lungs (pulmonary hypertension)

‘Our understanding of plaque instability may be extended to vein graft atherosclerosis, which appears to represent the end of a continuum of plaque instability. Compared with plaque in native coronary arteries, vein graft atheroma is more diffuse and vulnerable to rupture, and the consequences of plaque rupture in vein grafts seem to be associated with almost certain thrombotic occlusion within 7 to 12 years after surgery.’ [http://www.onlinepcd.com/article/S0033-0620\(02\)70017-0/abstract](http://www.onlinepcd.com/article/S0033-0620(02)70017-0/abstract)

As can be seen from this, if you take a vein from somewhere else in the body and use it in the heart as a bypass for a blocked artery (Coronary Artery Bypass Graft [CABG]), it is exposed to far higher blood pressure than it is designed for. In general CABGs last only a few years before becoming completely blocked by a large atherosclerotic plaque.

Atherosclerosis in pulmonary arteries/veins is far less common than atherosclerosis in veins used as bypass grafts, even when there is pulmonary hypertension (high blood pressure in the lungs). Probably

because, even in pulmonary hypertension the blood pressure never gets as high as in the larger arteries in the rest of the body. But it can happen, as outlined in this case history. *‘Primary pulmonary arteries atherosclerosis: discovering an unusual cause of death in forensic practice’*:

‘In the literature, there are few studies on atherosclerosis in the pulmonary artery in human beings and no cases similar to the one presented has been reported until now. The aim of the study is to describe a particularly unusual case of primary severe pulmonary atherosclerosis, in a 40-year old man...

Case presentation: *The patient had marked atherosclerosis in the pulmonary trunk and its branches, probably caused by a series of hemodynamic and endothelial changes, subsequent to the pulmonary hypertension.’ Rom J Leg Med [20] 177-180 [2012]*

As can be seen from these examples, if you raise the blood pressure in a blood vessel that does not normally, ever, develop atherosclerosis, then atherosclerosis will develop. That is simple cause and effect. And the mechanism underlying it appears very straightforward. Increased biomechanical stress, damaging endothelial cells leading to repeated thrombus formation.

From this it seems clear that endothelial damage is the key event for the entire process. With a healthy and intact endothelial layer, none of the other processes, e.g. thrombus formation can occur to cause a plaque to start, and develop. And the single most important cause of endothelial damage is biomechanical stress. Without that, nothing happens. Which is why veins, and blood vessels in the lungs, never become atherosclerotic.

The next steps

If we assume that, in everyone, endothelium is being damaged in areas of high biomechanical stress, what makes the difference between plaques developing and growing, and nothing happening? Or, to put this another way. What are the possible ‘causes’ of CVD.

Using broad brush strokes, we can split the causes into three main system. Those that occur at:

- Initiation
- Development

- Repair

Initiation

By initiation I mean those factors – on top of biomechanical stress - that will increase endothelial damage, or make endothelial damage worse when it occurs.

One of the most extreme example of a factor that induces endothelial damage is Kawasaki's disease.

'Kawasaki disease (KD) is a systemic vasculitis of childhood with widespread vascular endothelial damage in the acute stage. Long-term complications, such as myocardial infarction and death, are recognized.' <http://www.ncbi.nlm.nih.gov/pubmed/8901658>

In Kawasaki's there is significant, if short term, endothelial damage. It is associated with a far higher death rate from CVD, and heart attacks can occur in very young children in some cases as young as three. However these are often due to ruptured aneurysms, normally thought to be a late stage manifestation of atherosclerosis, rather than classic blockage due to thrombus formation.

Another 'inflammatory' condition that damages endothelial cells is Systemic Lupus Erythematosus (SLE). Young women with SLE have a fifty-five fold (relative) increase in the risk of dying of heart disease. To put that in another way, that is a 5,500% increase in risk. <http://www.ncbi.nlm.nih.gov/pubmed?term=9048514>

The main reason for this risk is almost certainly due to significant damage to the endothelial cells – as outlined in a paper called *'Imbalance between Endothelial Damage and Repair: A Gateway to Cardiovascular Disease in Systemic Lupus Erythematosus.'* [Sorry, there is a lot of jargon here, but two points are being made. In SLE there is a whole series of 'factors' that can, and do, damage the endothelium]:

'....endothelial dysfunction, one of the earliest steps of atherogenesis, has been demonstrated to occur in lupus patients even when they are naïve for cardiovascular disease. Currently known "endothelium-toxic" factors including type 1 interferon, proinflammatory cytokines, inflammatory cells, immune complexes, costimulatory molecules, neutrophils extracellular traps, lupus-related autoantibodies, oxidative stress, and dyslipidemia, coupled with the aberrant functions of the endothelial progenitor cells (EPC) which are crucial to vascular repair; likely tip the balance

towards endothelial dysfunction and propensity to develop cardiovascular disease in lupus patients.'
<http://www.hindawi.com/journals/bmri/2014/178721/>

This paper also mentions another key point – which is somewhat jumping ahead here. Namely that in SLE there is severe dysfunction of EPC function. This doubles the problem. Not only are mature endothelial cells under attack from many different toxins, the repair cells (EPCs) do not work properly.

Of course, Kawasaki's and SLE could be considered extreme conditions, with extreme effects on endothelial cells. They also create a short term increase in the risk of death from CVD. As does, incidentally, rheumatoid arthritis where, once again, we see significant endothelial damage/vasculitis, and a very high risk of CVD.

However, there are many other factors that can 'damage' the endothelium to a lesser degree [I am not referencing this list. I simply suggest going to Google and typing in endothelial damage followed by, any of the factors listed below]:

- Raised blood sugar levels/diabetes
- Cortisol (a key stress hormone)
- Cigarette smoking
- Air pollution
- Raised insulin levels
- High homocysteine levels
- Low levels of vitamin D
- Cocaine use
- etc.

In fact, this is a very simple game to play. If you can find any factor that increases endothelial damage, you will find that it is associated with an increased risk of CVD. Perhaps not the same increased risk in all populations with each factor. Equally, although all of factors listed above

damage the endothelium, they do so to very different degrees. And so the increased risk can vary a few percentage points, in the case of air pollution, to 5,500% with SLE.

Development

Once endothelial damage has occurred, and a thrombus has been created, there are related factors that can become involved to build bigger and potentially more damaging blood clots. Very large clots can, of course, completely block arteries, and they can be fatal very early on in the disease process. There have even been cases of people dying of heart attacks, and strokes, due to a single large blood clot in an artery – with no underlying plaque at all. This is relatively uncommon, but far from unknown.

In general, however, the final clotting event takes place where there is a relatively large plaque that has already formed. And plaques can take years, even decades, to do so. Clot upon clot, repair upon repair and then, a major and fatal thrombosis. This would be the ‘normal’ sequence of events.

Whilst the development of plaques is primarily dependent on repeated endothelial damage, other factors can exacerbate the formation of bigger and more difficult to repair clots. For example, raised blood clotting factors such as: fibrinogen, antiphospholipid syndrome, factor V Leiden, raised Lp(a). With any of these blood clotting abnormalities you are more likely to die from CVD

If we look at, say, antiphospholipid syndrome (APS) a.k.a. Hughes syndrome. This is an autoimmune disease, in which ‘antiphospholipid antibodies’ react against proteins that bind to plasma membranes. It is more common in women than in men. The exact cause is not known, but the main abnormality is activation of the clotting system. with thrombosis and vascular disease.

‘A major cause of morbidity and mortality in the context of the APS is the occurrence of thrombotic events, which may affect any arterial or venous vascular bed. Manifestations are common in these patients: deep vein thrombosis, pulmonary thromboembolism, stroke, transient ischemic attack, and coronary artery disease.’ <http://www.hindawi.com/journals/jir/2014/621270/>

The treatment is lifelong anticoagulation. Unfortunately, this is normally started after someone has had a major CV event, and is subsequently found

to have APS.

If we look purely at heart disease (CHD), perhaps the most important single clotting factor here is fibrinogen. In the Scottish Heart Study it was found that a high fibrinogen levels can increase the risk of CHD by over 300%.

'Fibrinogen is a strong predictor of coronary heart disease, fatal or non-fatal, new or recurrent, and of death from an unspecified cause, for both men and women.... Comparing the two extreme fifths, the hazard ratios for coronary death are 3.01 and 3.42, and for all-cause mortality are 2.59 and 2.20, for men and women respectively.' <http://www.ncbi.nlm.nih.gov/pubmed/9503176>

Both APS and raised fibrinogen represent long-term/chronic risk factors (although fibrinogen can also be more transiently raised in stress, anxiety, smoking and depression). However, factors that raise blood clotting risk in the short term also increase CVD risk. For example, bacterial infection. It has long been known that bacterial infection greatly raises the short term risk of death from CVD. This is almost certainly due to the fact that bacteria can stimulate blood clotting directly.

'It has long been known that blood often coagulates during sepsis or bacterial infections, but this has generally been regarded as a host's immune and inflammatory response. It also has been known that bacteria can activate factors that precede coagulation, but it had not previously been known that bacteria can pass the coagulation threshold and cause blood clots to form. Once they form, the clots can grow and propagate. Although this may help prevent the dissemination of the bacteria through the host, it often leads to serious vascular damage due to blocked and injured blood vessels.' <http://www.sciencedaily.com/releases/2008/11/081102154519.htm>

Just to look at one other factor, cocaine use. This both damages the endothelium and stimulates the entire blood clotting system.

'Our results demonstrated that chronic cocaine consumption alters several functions of the endothelium towards a pro-thrombotic condition and that some of those functions remain abnormal even after short-term drug withdrawal. These observations support the notion that endothelial dysfunction may play a key role in the pathogenesis of ischemic vascular disease observed in cocaine abusers.' <http://www.ncbi.nlm.nih.gov/pubmed/21601240>

'In addition to systemic and coronary vascular changes, cocaine has been found to cause alterations in platelet function and coagulation, with multiple cases reported of acute coronary artery thrombosis after cocaine use.' <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228621/>

Once again, it would be possible to go on, outlining factors that are thrombophilic (stimulate blood clotting) that also increase the risk of CVD. There are many of them, but the general point is straightforward. Any factor that increases the risk of blood clotting is likely to cause CVD. Either chronic plaque growth, or acute episodes of blood clotting.

On the other hand, we can look at a couple of conditions that reduce blood clotting, and protect against CVD.

Two of the most common would be Haemophilia and Von Willebrand disease. Both are genetic conditions where there is a lack of various clotting factors, and an increased risk of bleeding. This can obviously bring other health problems, but both have clear benefits in CVD.

'In a survey among all haemophilia patients in The Netherlands, the Standardised Mortality Ratio (SMR) for cardiovascular mortality was 0.2.' doi:10.1160/TH10-07-0460 *Thromb Haemost* 2011; 105: 274–278

A standardised mortality ratio of 0.2 means that the risk of dying is 20% that of the surrounding population. Another way to frame this is that haemophilia represents a fivefold reduction in risk of dying of CVD. Since synthetic clotting factors have been made available, the reduction in risk of CVD has attenuated.

In Von Willebrand Disease there is a significant reduction in the clotting factor known as Von Willebrand factor (VWF)). This stimulates platelet adhesion, a key process in the creation of thrombi. Patients with this condition have a greatly reduced risk of both stroke and death from heart attacks. Around a fifty per cent reduction in total CVD risk. <http://www.ncbi.nlm.nih.gov/pubmed/23506463>

Repair

After endothelial damage has occurred, and a blood clot has formed, the next stage is repair. This is normally achieved through a combination of EPCs covering over the thrombus, followed by a clear up operation, primarily coordinated by monocytes and macrophages. Therefore, anything that interferes with this will most likely increase the risk of CVD.

There are a number of conditions that reduce the production of EPCs. Probably the most important of these is age. As people get older the

synthesis of EPCs in the bone marrow reduces. Which could well explain why CVD kills far more older people than younger people, with the death rate accelerating in an almost logarithmic progression.

Other things that damage EPC production are chronic kidney disease (CKD). This is associated with a greatly increased risk of CVD.

'Most data available support the notion that EPC numbers and function are reduced in CKD patients, and this altered EPC biology may contribute to the high cardiovascular burden of CKD patients due to compromised reparative processes in the vascular system.'
<http://ndt.oxfordjournals.org/content/25/2/341.full>

Obstructive sleep apnoea (OSA) is another condition where EPC production is impaired. OSA is a condition where people, basically, stop breathing at night for periods of time. It is quite common, and it is associated with an increased risk of CVD.

'In most studies (in OSA), a reduction in circulating EPCs has emerged. The possible mechanisms underlying the decrease in the number or function of EPCs include prolonged inflammation response, oxidative stress, increased sympathetic activation, physiological adaptive responses of tissue to hypoxia, reduced EPC mobilization, EPC apoptosis, and functional impairment in untreated OSA.' <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3804572/>

As before, if a factor can be identified that damages the normal EPC development, or function, there will be an increased risk of CVD.

Obviously, there are many other aspects to 'repair' when it comes to plaques. Perhaps the most important is the healthy and efficient functioning of monocytes and macrophages. Both of these white blood cells have a crucial function in clearing up damaged tissue, bacteria, viruses and the like. The macrophage primarily by invagination. A process by which the macrophage will first oxidize the material – often to kill it – it then grows around the material to pinch it off, then ingest it.

Putting it very simply, macrophages eat the plaque and remove it. Macrophages and monocytes work closely in unison to achieve this – macrophages develop from monocytes.

So, anything that can interfere with the effective functioning of monocytes and macrophages will mean that the clear up process does not work so well and the plaque will grow faster. In fact, within large plaques you will often find large bloated macrophages, called 'foam cells' which

have lost the ability to digest anything more, or even move. Some of these macrophages simply split apart, and die.

'Macrophage apoptosis (death) is an important feature of atherosclerotic plaque development. Research directed at understanding the functional consequences of macrophage death in atherosclerosis has revealed opposing roles for apoptosis in atherosclerotic plaque progression. In early lesions, macrophage apoptosis limits lesion cellularity and suppresses plaque progression. In advanced lesions, macrophage apoptosis promotes the development of the necrotic core, a key factor in rendering plaques vulnerable to disruption and in acute luminal thrombosis (a heart attack).'

Again, things are not completely straightforward. At a certain, early, stage of plaque development macrophage death can protect from plaque growth. Later on, it can be very damaging.

Does the atherothrombotic theory fit the facts?

Clearly, any scientific hypothesis should fit with observed facts, and should not be contradicted by them. Contradiction, or confirmation, is notoriously difficult to achieve in absolute terms in medicine, as there are often so many variables in play (known and unknown).

For example, the cholesterol hypothesis is currently the most widely accepted hypothesis about heart disease. Namely that LDL-C, when the level is high, is absorbed into the arterial wall, causing inflammation and plaques. This hypothesis appeared to have been very strongly supported by the fact that statins – which lower LDL-C – also reduce the risk of CVD. Many people feel that this evidence was, in fact, overwhelming proof of the cholesterol hypothesis. (Even if other LDL-C lowering agents have not shown any benefit).

However, it is more likely that statins actually operate in a complete different way. It has been found, in many studies, that statins promote NO synthesis in endothelial cells, they also increase EPC production and function:

'Statins are potent drugs with a variety of cardiovascular protective effects which appear to occur independent of cholesterol reduction. The vasculoprotective effects of statins might be due to their direct effect on endothelial cells leading to improved nitric oxide (NO) bioavailability....The functional improvement and increased homing capacity of endothelial progenitor cells induced by statin treatment might reverse impaired functional regeneration capacities seen in patients with risk

factors for coronary artery disease or documented active coronary artery disease.'
<http://www.ncbi.nlm.nih.gov/pubmed/15238818>

Indeed, the effects of statins, when viewed in a different way, support the atherothrombotic hypothesis of CVD more powerfully than the cholesterol hypothesis.

In fact, every pharmaceutical agent found to significantly reduce the risk of CVD either protects the endothelium, reduces the propensity of blood clotting or improves EPC production or function. A non-exhaustive list would be:

- Aspirin
- Clopidogrel
- Warfarin
- Statins
- Ace-inhibitors
- tPA

On the other hand, drugs that increase blood coagulation increase the risk of CVD. For example:

- Steroids/corticosteroids
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Proton Pump Inhibitors (PPIs) – they reduce NO synthesis in endothelial cells
- Avastin (a cancer drug)

Avastin is particularly interesting, in terms of this discussion, in that it inhibits a substance known as Vascular Endothelial Growth Factor (VEGF). Endothelial progenitor cell production is stimulated by vascular endothelial growth factor-A (VEGF-A)

<http://www.ncbi.nlm.nih.gov/pubmed/24022223>

VEGF also stimulates endothelial cell maturation, and function and NO synthesis. So, it should come as no surprise to find that Avastin increases the development of atherosclerotic plaques, and also increases the risk of heart disease.

'Systemic VEGF inhibition disrupts endothelial homeostasis and accelerates atherogenesis, suggesting that these events contribute to the clinical cardiovascular adverse events of VEGF-inhibiting therapies.' <http://www.ncbi.nlm.nih.gov/pubmed/23561917>

Moving away from the effects of drugs. Does the atherothrombotic hypothesis fit observations of various diseases? As previously mentioned diseases that create endothelial damage also increase the risk of CVD, e.g. SLE, Rheumatoid arthritis and Kawasaki's. Diseases that increase blood coagulation also increase the risk of CVD e.g. Hughes disease and Factor V Leiden. Diseases that damage EPC production increase the risk of CVD e.g. Chronic Kidney Disease and many forms of cancer.

However, probably the most important disease – in terms of sheer numbers – is type II diabetes. It has been observed that type II diabetes increases the risk of death from CVD by a factor of three, in men, and a factor of five, in women.

As you might expect, people with type II diabetes have significant endothelial dysfunction. This may not be due to the raised blood sugar levels themselves:

'Both insulin resistance and endothelial dysfunction appear to precede the development of overt hyperglycemia in patients with type 2 diabetes. Therefore, in patients with diabetes or insulin resistance, endothelial dysfunction may be a critical early target for preventing atherosclerosis and cardiovascular disease.' <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2350146/>

However, endothelial function is a key abnormality in type II diabetes and, in part, explains the raised risk of CVD. But of course, type II diabetes also creates a pro-thrombotic state with many different clotting factors raised, and there is a significant reduction in EPC numbers. So, type II diabetes creates all of the factors needed to increase CVD risk.

Finally, to look at stress. This is a vast subject which I will not look at in any great detail here. I will split stress into acute and chronic. Acute stress can be physical, or psychological. Chronic stress tends to be psychological.

In both case the 'flight of fight' system is activated. This has a wide

range of different effects. Raised blood pressure, increased heart rate, diversion of blood supply from the GI tract to muscles. Raised blood sugar levels. All physiological systems are affected on one way or another. It should come as no surprise to find that in a situation of acute psychological, or physical stress, the blood becomes hypercoagulable.

'Stress-induced activation of the sympathoadrenal medullary system activates both the coagulation and fibrinolysis system resulting in net hypercoagulability. The evolutionary interpretation of this physiology is that stress-hypercoagulability protects a healthy organism from excess bleeding should injury occur in fight-or-flight situations.'
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4386736/>

So, it should be no surprise to find that acute psychological stress often immediately precedes heart attacks (myocardial infarction)

'Observational studies have found repeatedly that patients report excessive anger, anxiety, sadness, grief, or acute stress immediately prior to onset of MI, and recent meta-analyses summarizing these findings reported strong associations between MI occurrence and many of these acute emotions.' <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3549526/>

This should not be surprising and, in fact, with the widely accepted knowledge that the final event in a heart attack is the sudden development of a blood clot, that blocks a coronary artery. In fact, this observation fits with both the cholesterol hypothesis and the atherothrombotic hypothesis.

Acute physical stress can also induce blood clotting, and an increase risk of heart attacks. As can getting up in the morning. A time when stress hormones increase blood coagulation.

'Myocardial infarction occurs most often in the early morning hours, perhaps partly because of the increase in catecholamine-induced platelet aggregation and increased serum concentrations of plasminogen activator inhibitor-1 (PAI-1) that occur after awakening.'
<http://emedicine.medscape.com/article/155919-clinical>

Indeed, there is no dispute that acute physical and/or psychological stress are very important triggers for heart attacks and strokes.

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Chapter Thirteen

Statins and Cancer: Cause or Cure?

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Abstract

Statins have been referred to as “miracle drugs” because they not only prevent coronary heart disease, but may also reduce the risk of unrelated diseases like Alzheimer’s and cancer, despite evidence that the reverse might occur. Any alleged benefits are usually attributed to diverse immunomodulatory, anti-inflammatory, anticoagulant and other pleiotropic effects of statins. Interfering with cellular cholesterol synthesis could theoretically play a role in some malignancies; *in vitro* studies have shown statins to exhibit anti-proliferative properties mediated by a statin induced reduction in mevalonate and downstream geranylgeranylated proteins. However, statins have other pleiotropic immunomodulatory actions that might promote existing cancer. Possible explanations for these conflicting views will be discussed, as well as the difficulty in proving any cause-effect relationship. Importantly, only well-designed prospective trials, free of industry sponsorship, will determine if statins cause or cure cancer

Are Statins Panaceas Or Poisons?

Opinions about statin efficacy and safety tend to be polarized because of the difficulty in obtaining accurate information on the incidence and prevalence of adverse side effects.

Symptoms like increasing forgetfulness, fatigue and inability to concentrate are often attributed to getting older. The incidence of prostate and other cancers also increase with age.^{1,2} In addition, many statin patients, particularly the elderly, frequently take multiple medications that might increase or decrease susceptibility to side effects such as cancer. Adverse side effects of drugs are frequently minimized or concealed in drug

company sponsored clinical trials^{3a,4a}. Adverse drug side effects are frequently minimized or ignored in drug company sponsored clinical trials^{3b,4b} and cancer may not surface until decades after a statin has been approved⁵. Symptoms are not recognized as side effects. In one study, almost 4% of all hospitalizations were due to adverse drug reactions that were not recognized by the attending physicians at the time of admission⁶. When patients inquire about the possibility that a statin is causing their problem, physicians often deny or dismiss this as being very unlikely or impossible, even when there is no other plausible explanation⁷. This would be more apt to occur with cancer since publications can be cited to support their opinion.

Studies that do show a likely causal relationship (or are critical of statins and the theory that cholesterol causes coronary disease) are difficult to publish because medical journals do not want to lose their lucrative profits from drug company reprints and advertisements⁸. Studies sponsored by the pharmaceutical industry are also more likely to be published in higher impact factor journals than are studies without industry funding⁹. Only a very small percentage of statin side effects are reported to MedWatch, the FDA Adverse Event Reporting System (FAERS). The majority comes from pharmaceutical companies because regulations mandate this and there are costly penalties for noncompliance. Reporting by health care professionals and consumers is voluntary and only 27 states require hospitals to notify their health departments of adverse drug side effects. There are numerous other criticisms of the current reporting system^{10,11}. Side effects shown to be due to statins are not reported by physicians to avoid lawsuits and unfavorable publicity.

Numerous studies from around the world confirm the association between low cholesterol and the subsequent increased risk of various cancers^{12,13,14,15,16,17,18,19,20,21,22}. As previously noted, all statins are carcinogenic in laboratory animals but whether this is a direct effect or related to cholesterol lowering is not clear²³. Because of this and other disabling side effects, many people consider statins to be poisons that should be avoided at any cost. At the other end of the spectrum, enthusiasts believe that statins are so safe they should be added to the water supply like fluoride or given to everyone 50 or older²⁴.

Are Statins The Holy Grail For Cancer?

That was the title of an editorial by Mayo Clinic authorities²⁵ who cited meta-analyses and observational studies showing that statin use was associated with reduced risk of prostate, hepatocellular and esophageal cancer^{26,27,28,29}. How these benefits are achieved is not clear, but it is suggested that in addition to lowering cholesterol, statins may exert antineoplastic effects through blockage of mevalonate and other pathways, or proapoptotic, antiangiogenic, and immunomodulatory effects that prevent cancer growth^{30a,31a}.

Support comes from a *New England Journal of Medicine* article that studied the relationship between statin use prior to cancer diagnosis and cancer-related mortality in the entire Danish population from 1995-2009 in adults over the age of 40. It found that statins were associated with a 15% reduction in cancer and all cause mortality in 13 malignancies, as well as improved survival in the four most frequent cancers; lung, colorectal, prostate and breast^{32a}. The authors also cited evidence that interference with cellular cholesterol synthesis may inhibit cancer growth and metastasis^{30b,31b,33,34}. In addition, statins have been linked to inhibiting key cellular functions and proliferation in cancer cells with resulting antiproliferative effects due to inhibition of key cellular functions in cancer cells^{31c,35}. Other studies also imply that in addition to prevention, statins can be used to treat cancer of the prostate^{36,37}, breast^{38,39} and kidney^{40,41}. It has been suggested that this may also be due to blockage of the mevalonate pathway since mevalonate has been shown to promote the growth of neoplastic and preneoplastic cells⁴².

However, a closer look at the study^{32b} suggests that higher baseline cholesterol levels might actually improve survival in patients with cancer. Baseline total cholesterol concentration of statin-treated populations is often higher than those of the general population⁴³. On the other hand, low plasma levels of low-density lipoprotein cholesterol have been shown to be robustly associated with an increased risk of future cancer⁴⁴. Moreover, in a long-term follow-up study, moderate total serum cholesterol was found to have a protective effect on 40-year cancer mortality⁴⁵, and an analysis of large statin randomized controlled trials demonstrated an inverse

association between on-treatment low-density lipoprotein cholesterol levels and incident cancer⁴⁶. Of note, in the Danish study^{32c}, the absence of a dose–response relationship for statins and cancer-related mortality, accompanied by an increase in cardiovascular mortality in statin-treated patients, clearly suggests that statin use selected the healthy statin user or unselected the unhealthy cancer patients with low cholesterol.

However, the National Cancer Institute (NCI) Fact Sheet indicates that it is funding a study to determine whether lovastatin can reverse precancerous changes in atypical or dysplastic nevi to prevent them from progressing to melanoma skin cancers⁴⁷. It also states that “Two large cardiovascular clinical trials have demonstrated a significant reduction in skin cancer among patients taking lipid-lowering drugs” and “various human trials and preclinical studies suggest that statins may have chemopreventive activity against skin cancer”. No references are provided to support this, and it is possible that statins are contributing to the current epidemic of nonmelanoma skin cancers⁴⁸. The agency is also funding a study on colorectal cancer based on a report that statins can reduce risk of this by 47%⁴⁹, despite numerous large-scale studies showing no such effect^{50,51,52}.

Immunomodulatory action of statins

In vitro studies have shown statins to exhibit anti-proliferative, pro-apoptotic, anti-invasive and radio-sensitization properties mediated by a statin induced reduction in mevalonate and downstream geranylgeranylated proteins^{53,54}. These pleiotropic effects of statins might actually prevent the initiation and promotion of cancer. However, statins have other pleiotropic actions that might promote existing cancer. For example, the short-term beneficial effect of statin therapy after cardiac transplantation has been attributed to a statin induced reduction in natural killer (NK) cell cytotoxicity⁵⁵. However, a chronic attenuation of NK cell function will decrease the innate cell-mediated immune response to tumor cells⁵⁶. It is known that statin therapy increases circulating bone marrow derived endothelial progenitor cells (EPCs) with enhanced functional activity⁵⁷. Although EPCs might augment the neovascularisation of ischemic tissue and wounds, they might promote tumor growth by supporting

angiogenesis^{58,59}. Not surprisingly, the levels of circulating EPCs correlate directly with the stage of invasive breast cancer, and circulating EPCs are significantly higher in stages III and IV when compared with stages I and II breast cancer patients⁶⁰. Likewise, circulating EPC levels are much higher in patients with aggressive compared with less aggressive non-Hodgkin's lymphoma⁶¹. Recently, statins have been shown to increase the numbers and functionality of peripheral regulatory T-cells (Tregs), *in vivo*, by inducing the transcription factor forkhead box P3⁶².

Among the various mechanisms involved in cancer development, mounting evidence has found that the dysfunction of the immune system may exert an important role. In a malignant environment, immune system homeostasis and control of self-tolerance are significantly altered. Tregs are immunosuppressive cells implicated in autoimmune diseases and malignant processes. They have suppressive functions against the autologous immune reaction, which in turn exerts a fundamental role in the immunosurveillance of malignant tumors. In fact, enhanced Treg numbers and functionality might impair the host anti-tumor immune response⁶³. Additionally, Tregs have been shown to promote the induction of alternatively activated monocytes/macrophages, which contribute to hampered anti-tumor immunity⁶⁴. Compared with normal controls, peripheral Treg numbers are increased significantly in cancer patients⁶⁵. In numerous solid tumor types, the accumulation of Tregs predict a reduction in patient survival^{66a}. In animal models, depletions of Tregs have resulted in total tumor rejection⁶⁷.

Therefore, even though the aforementioned immunosuppressive effects of statins might be beneficial in reducing inflammatory cells in arterial walls and promoting plaque stability, they might be detrimental by suppressing antitumor immune responses resulting in microscopic foci of tumor cells escaping dormancy and proliferating^{66b}.

Indeed, it appears that statins increase the risk of cancer in the elderly, who are more likely to harbor cancer cells because of their advanced age and associated immunosenescence⁶⁸. This was evident in several statin trials. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), cancer incidence was increased significantly in subjects randomized to pravastatin over the 3.2-year study period⁶⁹. The mean age at trial entry was 75 years, and the decrease in cardiovascular disease

mortality was offset by an equal increase in cancer mortality, resulting in unchanged overall mortality. The post hoc analysis of the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study demonstrated a significant increased cancer incidence in elderly subjects (65–75 years) randomized to pravastatin over the 6-year trial⁷⁰. Furthermore, a secondary analysis of the Treating to New Targets study demonstrated that subjects randomized to atorvastatin 80 mg daily exhibited a trend towards increased death compared to those randomized to atorvastatin 10 mg daily; the increase in death was largely from cancer⁷¹. It is certainly plausible that the immunomodulatory effect of statins explains the increase in cancer seen in elderly subjects exposed to statin therapy, and there may be a dose–response relationship.

Notably, immunosuppression represents an emerging risk factor for nonmelanoma skin cancer (NMSC). In fact, immunosuppressive treatments seem to act as a catalyst for skin carcinogenesis as they increase the frequency, number, and aggressiveness of such tumors. Recently, the characteristics of specific components of the immune system associated with the development of NMSC among organ transplant recipients have been highlighted⁷². It was reported that kidney transplant recipients with previous NMSC had a higher number of Tregs present in the peripheral circulation than recipients without NMSC. In addition, there was an overrepresentation of Tregs within NMSC removed from kidney transplant recipients compared with matched NMSC from patients who were not taking immunosuppressive treatments. Furthermore, during prospective follow-up, in the select group of transplant recipients who had previous NMSC and therefore were at high risk for new NMSC development, it was found that a high number of Tregs and low number of NK cells improved the accuracy of predicting a more than a six fold increased risk for developing a new NMSC. Disturbingly, the immunomodulatory pleiotropic actions of statins resemble the immune phenotype, which predicts risk for post-transplantation NMSC. Data from randomized trials with statins are revealing. A systematic review found moderate evidence of an increased incidence of NMSC (median risk ratio 1.6, range 1.2–2.2) with statin drugs^{73a}. Specifically, in the first 2 simvastatin trials, the Scandinavian Simvastatin Survival Study (4S)^{74a}, and the Heart Protection Study

(HPS)^{75a}, NMSC was observed more often in the treatment groups. In the 4S, there were 13 NMSC in the statin group (0.6%) and six (0.3%) in the placebo group^{74b}. In the HPS, in simvastatin-allocated participants there were 243 NMSC (2.4%) vs. 202 (2.0%) in placebo-allocated individuals^{75b}. The difference is statistically significant if the results from both studies are combined (in simvastatin groups, 256 of the 12,490 participants; and in control groups, 208 of the 12,490 participants; $P = 0.028$). After publication of the four trials included in the review^{73b}, NMSC have been excluded in all reports from subsequent statin trials for unknown reasons. Furthermore, an observational study from Finland has shown a standardized incidence ratio (SIR) for Merkel cell carcinoma (MCC) of 1.94 in ages 60–74 and a SIR of 3.16 in ages <60 years among statin users compared to statin nonusers, implying that statin therapy might be increasing the risk of MCC in atypically younger individuals⁷⁶. A similar phenomenon was noted in patients with immunocompromising states^{77,78}. Of note, MCC is a rare and aggressive neuroendocrine skin cancer associated with immunosuppression and a novel polyomavirus; its incidence has increased several fold in Denmark since the mid-1980s corresponding to the introduction and increasing use of statins in clinical practice⁷⁹.

Also women may be particularly sensible to the immunomodulatory action of statins. Among women randomized to pravastatin (mean age: 59 years) in the Cholesterol and Recurrent Events (CARE) study, a 5-year prospective randomized secondary prevention trial, breast cancer was significantly increased⁸⁰. Breast cancer occurred in 1 patient of 290 in the placebo group and 12 patients of 286 in the pravastatin group ($P < 0.002$) over the trial duration, and some of the cancers were recurrences. This was not reported in other prospective statin trials, but it is of concern since there are observational data suggesting an increase in breast cancer of 28% among elderly women on statin therapy > three years⁸¹. It has been recently reported that higher 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMG-CoAR) expression in breast cancer cells, *in vivo*, is associated with a less aggressive phenotype⁸². Therefore, the inhibition of HMG-CoAR by statins might increase the aggressiveness of breast cancer. Additionally, statins have been found to activate PI- 3K and ERK1/2 signaling pathways,^{83,84} which could promote the invasive growth of ductal

carcinoma in situ⁸⁵. These data are particularly disturbing since the prevalence of microscopic breast cancer at autopsy has been reported to be 39% among women 40–49 years dying without clinically diagnosed cancer⁸⁶. A population-based case–control study of long-term (≥ 10 years) statin use among postmenopausal woman showed a two-fold risk of developing both invasive ductal and lobular breast carcinoma compared with never users of statins⁸⁷. Moreover, in a recent case–control study, it was found that statin use was associated with thyroid cancer in female patients⁸⁸.

Finally, mounting evidence has found that statin therapy can lead to new-onset of diabetes^{89a}. Interestingly, certain groups of patients are at particular increased risk for statin induced diabetes; they include both women^{89b,90} and the elderly^{89c}. Long-term observational data have indicated that diabetes is positively and significantly associated with all-cause and cancer mortality⁹¹. Also prediabetes has been shown to be associated with an increased risk of cancer⁹². Furthermore, statin therapy has been associated with an increase in fasting blood insulin levels^{89d}, and chronic hyperinsulinemia can lead to increased expression of insulin-like growth factor-1 which has mitogenic effects⁹³. Therefore, it is also possible that people prescribed long-term statin therapy might be at increased risk of cancer resulting from the off-target diabetogenic and hyperinsulinemic effects of these drugs.

Conclusions

We express concerns on the use of statins to prevent cardiovascular disease in certain segments of the population. They include the elderly, women and those individuals with a clinical history of cancer. Primary and secondary prevention trials largely have excluded patients with a history of cancer. In real practice situations, statins are commonly used in patients with prevalent cancer. We feel this is a leap of faith, and the shorthand long-term safety of these agents needs further prospective evaluation among patients with a history of cancer. It is unlikely that trends will be noticed as these drugs are routinely used in clinical practice, since the reporting of side effects of drugs is incomplete and the prevalence of cancer is large. Likewise, more

prospective data need to be produced on the safety of statins in the elderly and immunodepressed population, who are more likely susceptible to the immunosuppressive and tumor promoting effects of statins, because of their immunosuppressive state and increased chance of harboring microscopic foci of cancer cells. Equally important, more prospective data are needed on the safety of statins in women and people at risk to develop diabetes, and high-dose statin use, in general.

Key issues

- Low cholesterol has been shown to be associated with an increased risk of cancer in numerous studies although it is difficult to prove this as well as other cause-effect relationships.
- Statins are carcinogenic in laboratory animals with blood levels similar to those seen in clinical practice.
- *In vitro* studies have shown statins to exhibit anti-proliferative properties.
- Other studies report that statins prevent risk of prostate, hepatocellular and esophageal cancer or can be effective in treating these and other malignancies.
- It has been demonstrated that these and other alleged statin benefits are due to purported pleiotropic effects rather than lipid lowering.
- Statins have other pleiotropic immunomodulatory actions that might promote existing cancer.
- Therapy guidelines have replaced lowering LDL cholesterol as a goal with an arbitrary 10-year risk assessment that would make tens of millions of additional individuals eligible for treatment.
- Statin trials have typically randomized subjects free of prevalent cancers and have been about 5 years in duration. Long-term follow-up data are limited, particularly for the development of cancer.
- More prospective data need to be produced in particular segments of

the population on the safety of statins who might be more likely susceptible to the immunosuppressive and potentially tumor promoting effects of statins

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Chapter Fourteen

Deciphering The Dilemma Of Perilous vs. Pleiotropic Effects Of Statins

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Abstract

Statins became the best selling and most profitable drugs ever because they purportedly safely lowered cholesterol, which was presumed to be the major cause of coronary atherosclerosis. Subsequent studies showed that the benefits of statins were limited to patients with a history of a heart attack and that they were not related to either cholesterol or LDL levels or their degree of lowering. The explanation for this was that statins reduced inflammation and clot formation in addition to other “pleiotropic” effects such as improved endothelial nitric oxide formation, stabilization of atherosclerotic plaque and improved immune system function. Pleiotropy refers to the observation that a gene or drug may have two or more apparently unrelated effects. These can be desirable as well as undesirable, but with respect to statins, “pleiotropic” has become a synonym for “beneficial”. For example, it has been claimed that statins also reduce the risk of various malignancies, despite the fact that all statins are carcinogenic in rodents at doses similar to those used to lower cholesterol in patients. In addition, as indicated in other chapters, statin trials show an increase in breast and skin cancers, which would be the first to be detected clinically. Similarly, it has been suggested that statins may prevent or even be used to treat Alzheimer’s disease since some studies show that patients on statins are much less likely to develop this disabling dementia than controls taking a placebo. The relevant literature not only contradicts this, but statin labels must now include a warning about adverse responses such as memory loss and confusion. There are no known pleiotropic effects of statins that might influence the onset or course of Alzheimer’s and the best explanation for this discrepancy may be that the cohort on statins likely had high

cholesterol levels for years that had a protective effect. Studies show that elderly patients with high cholesterol and LDL levels are also protected from infectious diseases and live the longest. The latest guidelines for statin therapy no longer have lowering LDL as much as possible as a goal, but target those at increased risk . This is based on arbitrary criteria of age, gender and past history that would now make an additional 12 million Americans eligible for statins. Cholesterol is not even mentioned and for some reason, family history of premature death due to coronary disease is not included. On the other hand, all type 2 diabetics over the age of 40 should be treated, despite evidence that statins cause diabetes and the warning labels also now also include this. Canada and other countries also mandate a warning that statins lower Coenzyme Q10, which “could lead to impaired cardiac function in patients with borderline congestive heart failure.” This is a particular problem in the elderly that can be prevented and treated with CoQ10 supplements. Statin manufacturers are well aware of this and Merck was granted 2 patents in 1990 for a statin Q10 combination, “to help prevent the inflammation to come.” Such drugs were never made or marketed since they would have called attention to adverse side effects and blemish the widespread belief that statins were extremely safe. Merck’s patents also prevented any other company from marketing a statin CoQ10 combination. Such adverse effects are never included in discussions of statin pleiotropy for obvious reasons, and it is likely they will continue to be used to prevent or treat disorders in which they are more apt to do harm than good.

The Demise Of The Diet-Heart Hypothesis

The belief that fatty foods and cholesterol caused coronary atherosclerosis stemmed from experiments 100 years ago demonstrating that feeding cholesterol and saturated fat to rabbits caused their blood cholesterol to skyrocket and produced fatty deposits in arteries similar to atherosclerotic plaque in humans. Five decades later, Ancel Keys reported a close correlation between saturated fat intake, cholesterol levels, and deaths from coronary disease. As a consequence, everyone was urged to sharply restrict eggs, butter, other dairy products and fatty meats. However, these studies were flawed and the stellar success of statins is more of a tribute to

promotional hype than progress in improving health. The problem is that since rabbits are herbivorous, cholesterol and saturated fat are foreign substances and these results could not be reproduced in rodents and other meat eaters. Keys had data on 21 countries but cherry-picked the six and later seven that best supported his theory.^{1,2} Had he reported on all the data available, there would have been no correlation between diet, cholesterol and coronary mortality, and if he selected countries like Israel, Sweden, Germany and France, he would have concluded that the more saturated fat and cholesterol consumed, the lower the incidence of deaths from coronary heart disease.³ And a 30-year follow-up of Framingham participants found that for each 1% drop in cholesterol, there was actually an 11 % **increase** in coronary and total mortality.⁴

The “Prudent Diet” study launched in 1957 compared two groups of healthy 49 to 59-year-old New York businessmen. One group followed a restricted diet with corn oil and margarine instead of butter, cold cereal rather than eggs, and chicken and fish to replace beef. The control group ate eggs for breakfast and meat three times per day. The results published a decade later revealed that although cholesterol levels of those on the restricted diet averaged 30 points lower than controls eating eggs and meat, they had eight deaths from heart disease compared to none in the controls. Similar trials also failed^{5,6}

The World Health Organization’s Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study that began in 1971 involved thirty-two centers in twenty-one countries that monitored approximately ten million men and women aged 25-64 for ten years.⁷ It found that the eight lowest saturated fat consumption countries had the highest CHD death rates and the eight highest saturated fat consumption countries had the lowest rates of CHD deaths. A Framingham follow-up study similarly showed that the more saturated fat and the more cholesterol people ate, the lower their serum cholesterol was.⁸ The NIH Women’s Health Initiative (WHI) study that started in 1991 was a 15-year project conducted at 40 clinical centers involving 161,808 healthy postmenopausal women.^{9,10} One component of this evaluated the effect of a low-fat and high fruit, vegetable and grain diet on the prevention of CHD, compared to a control group that followed their usual eating habits. Although there was some lowering of blood lipids in the

low fat intervention group, there was no reduction in CHD or stroke. In addition, over two-dozen studies have reported that coronary heart disease patients ate less or the same amount of saturated fat as healthy controls.

Cholesterol Does Not Cause Heart Disease & Statins Don't Work By Lowering Lipids

If cholesterol caused coronary atherosclerosis, then people with higher levels should have more coronary disease and lowering cholesterol should have the reverse effect. However, no association between cholesterol levels and the severity or extent of atherosclerosis has ever been found in postmortem studies of the general population. In familial hypercholesterolemia, there is no association between the very high cholesterol and LDL levels and a corresponding increased incidence or prevalence of coronary disease. Nor is LDL-cholesterol higher in those with heart disease compared to controls with no history of this.^{11,12} No clinical or imaging study has found any relation between the degree of cholesterol lowering and improvement. In one angiography study in which blood cholesterol had been reduced by more than 25% in 24 patients, atherosclerosis was increased in 18 and unchanged in eight. A Mayo Clinic study similarly found that in all patients whose cholesterols had decreased by more than 60 mg., there was a significant increase in coronary atherosclerosis. High cholesterol does not increase risk for heart attacks in senior citizens, women of any age, as well as patients with diabetes or renal failure.

If statins prevented CHD by lowering cholesterol, one would expect to see a clear cardioprotective dose-response relationship but this has not been demonstrated, even in patients who have had a heart attack. Nor have statins been proven to prevent coronary events and deaths in people with no history of heart disease.¹³ This is extremely important since new therapy guidelines no longer have lowering LDL as much as possible as the goal, but rather an arbitrary 10-year risk assessment of 7.5% or more.¹⁴ This would put millions of healthy people on statins, including all diabetics 40 and older, despite the fact that statins can trigger diabetes and make it more difficult to control. A non-smoking, non-diabetic 70-year-old African American woman with fabulous numbers: total cholesterol 175, good HDL

90 and a systolic blood pressure of 115 would still require moderate to high dose statin therapy perpetually. Dutch researchers who have been following senior citizens since 1997 found that 100% of men and 65% of women would have been prescribed statins based on their risk level. Examination of the data showed that only 12.7% of men and 7.9% of women actually had a heart attack or stroke. It seems doubtful that statins would have prevented this.

Inflammation And The Beneficial Pleiotropic Side Effects Of Statins

The new statin treatment guidelines tacitly acknowledge that statins don't work via effects on lipids or lipoproteins. Cholesterol and HDL are not even mentioned and LDL is not a concern unless it is over 190 mg/dL. As a result, it is now claimed that the benefits of statins in coronary heart disease, as well as a host of unrelated disorders, are achieved by pleiotropic properties such as reducing inflammation, clot formation, platelet aggregation, angiogenesis, oxidative stress and sympathetic nervous system hyperactivity, as well as improving endothelial function and nitric oxide levels, stabilizing atherosclerotic plaque and immunomodulation.¹⁵

Anti-inflammatory effects seem to be the most important since inflammation is now viewed as the major cause of coronary atherosclerosis and has been implicated in Alzheimer's disease, various malignancies and other non-lipid related disorders that statins can allegedly prevent. The problem is that the Justification for the Use of Statins in Primary Prevention (JUPITER) trial, showed that statins differed in their ability to reduce inflammation, which was defined as an elevated C-Reactive Protein (CRP), and that this was not related to their effects on lowering LDL.¹⁶ It has also been proposed that in addition to being a mere marker of inflammation, CRP is a direct cause of cardiovascular disease,¹⁷ but how this applies to preventing Alzheimer's and cancer is not clear. To add to the confusion, there is considerable evidence that statins can cause these and other disorders they allegedly prevent, especially cancer.^{18a}

Why No Conclusions Can Be Drawn About Good Or Adverse Statin Side Effects

Most meta-analyses and reviews fail to find any significant adverse side effects of statins and a recent one claimed that aside from a small increase in new diabetes, there were no side effects.¹⁹ Some of the reasons for this include the fact that over 90% of side effects are not reported because they are not recognized, and even when they are diagnosed, doctors want to avoid litigation. Most statin trials are funded by drug companies that also oversee them, raw data is not available and side effects are ignored, minimized or not reported. Trials that are stopped because of statin side effects are also not reported. This is a particular problem with cognitive side effects, especially in the elderly, since memory problems, confusion and difficulty concentrating are usually attributed to old age. Even when patients report improvement in symptoms when off the drug and a recurrence if it or another statin is resumed, physicians usually deny any possibility of a causal relationship. Statins also differ with respect to cognitive side effects depending on whether they are lipophilic or hydrophilic.²⁰ The FDA recently added this black box warning, “There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).”

However, this is not an accurate assessment, since a search of the FDA Adverse Events Databases from 2004 to 2014 revealed 36,605 reports of statin related cerebral dysfunction including memory impairment, transient global amnesia, confusion, paranoia, disorientation, depression, and dementia related to statins. Since it has been estimated that less than 2.5% of statin side effects are reported, this represents well over 3.5 million people. Many of these side effects are not reversible, and an episode of global amnesia lasting 6 to 10 hours could be fatal for someone flying a plane or operating heavy machinery. Baycol was withdrawn because of a high incidence of fatal cases of rhabdomyolysis, but all statins cause this. Although rarely mentioned there have been over 1,000 rhabdomyolysis deaths in the past 7 years, but the cause of death is listed as renal failure, the reason why most rhabdomyolysis patients die.

The above is just the tip of the iceberg. All statins are carcinogenic in rodents, but it may take decades for carcinogens to surface in humans, and most statin trials or follow-ups last less than five years. Nevertheless, an increase in nonmelanoma skin and breast cancers, which would be the earliest to diagnose, has already been documented.^{18b} This may just be the tip of the iceberg, and with long-term follow-up and improved reporting, neuropathy, an ALS like syndrome, cataracts and especially certain cancers may be added to the warning list. Everyone, especially healthy people, should be aware of this before complying with the new guidelines, which recommend higher statin doses that are likely to increase any adverse side effects.

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Chapter Fifteen

Critical Review Of Recent Drug Company

Sponsored Trials About Statin Efficacy And Safety

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Abstract

In 2005-2006, New Regulations were introduced in the conduct and publication of randomized controlled trials (RCT). This implies that before 2005, RCTs were less reliable than afterwards. To evaluate this, we reviewed studies testing the action of the cholesterol-lowering statins and conducted before and after 2005. The four studies published after 2005 were all testing rosuvastatin. Globally they show that rosuvastatin is not effective in secondary prevention, while the results in primary prevention are highly debatable. Furthermore, studies comparing statins to each other all show that none is more effective than any other, including rosuvastatin. This implies that statins are globally not effective in cardiovascular prevention, including in diabetic patients, and that the studies published before 2005 are probably flawed.

Introduction

A careful examination of the most recent statin trials and comparing them with “ancient” trials – those conducted before the 2005 *New Regulations of clinical trials* – reveals a striking discrepancy between the two categories; indicating that collectively and for years we have been very wrong regarding the miraculous health benefits of statins. Despite recent advances in clinical research transparency, there is still need of improving independent expertise and regulation as the present ones are not sufficient and should be reinforced. Two major questions relate to the real effects of drugs (both efficacy and safety) and to trial data secrecy. A corollary

question is how much transparency is enough. Full transparency means having access to the complete raw clinical data of each randomized patient. This should allow a rebuild of the original dataset, a remake of the statistical analyses from an individual patient basis, and a comparison with the data published by the investigators on one side and, on the other side, with those submitted to the Health Authorities by the industrial to obtain access to the market. Refusal to give access to these data may suggest that the industrial and/or the investigators have something to hide. Providing all the data is crucial to re-establish credibility and confidence.

To determine the clinical efficacy of a medical drug, a critical issue lies in the very quality of the randomized clinical trials (RCT) evaluating this efficacy. As drugs are commercial items, credibility of RCT data evidently depends on the credibility of the principal investigators in charge of conducting the RCTs. In particular, are they free of conflicts of interest, as for example financial links with the sponsor?

This concern is justified. As of today, the owner of the patent (very often an industrial) is usually still both sponsor and principal manager – or even investigator – of the RCT. This undermines the credibility of the overall RCT data and has led prestigious scientists to state that modern medical scientific data are generally irreproducible^{1a,2a,3a}, often wrong,^{4a,5a,6a,7a,8a} going as far as claiming that “*an estimated 85% of research resources are wasted*”^{1b,2b}.

One could argue that national and international institutions – as for instance the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) – are supposed to ensure that industry adequately conduct RCTs and fully report drug data regarding both efficacy and safety. However, there is no rigorous control. As an example, raw clinical data are still not available.

Apart from avoiding some rather “commercial” flaws^{9,10,11}, key measures in ensuring RCT quality are concealment of patient allocation and double blinding of patients and caregivers. A lack of respect of one of these obligations may introduce unintentional bias in RCTs, in particular when clinical efficacy is based on “soft outcomes” – such as nonfatal events, revascularisation or unstable angina, when evaluating cardiovascular drugs – or composite outcomes mainly including soft outcomes^{12a}. A clear

possibility of such an unintentional “*unblinding bias*” has been recently described^{13a}. The risk lies in undermining the credibility of RCT data and it is not exaggerated to say that we are facing an unprecedented wave of scepticism about medical sciences from both the public and the health professionals^{14,15}.

To check on this, we chose to focus on one of today’s most prescribed medicines, statins to lower cholesterol.

The present study was thus initiated with the aim to examine whether the most recent statin studies provide similar results – for both efficacy and safety – as the “ancient” ones. In case of discrepancy, what would be the explanation?

It is important to remember that there are two periods in the modern history of RCTs: before and after the 2005 *New Clinical Trial Regulations*. These were instated by the Health Authorities in Europe and USA – following in particular the Vioxx, Celebrex and other incidents – to bring the pharmaceutical industry into more transparency^{16a,17a,18a,19a,20a}.

Until 2005, being the sole depositories of the data yielded by the RCTs, industrialists were tempted to publish only what they chose to.^{3b,4b,5b} One scenario was frequent: up to a dozen of RCTs testing a new drug was set up in different countries, but then only those providing favourable data were published. If only one RCT turned out positive but all the others negative, either only the positive one was published and not the others; or the unfavourable RCTs were just prematurely discontinued, leaving the single RCT showing that the drug treatment was effective. This is known as a publication bias^{5c,6b}. Importantly, subsequent meta-analyses including data from various RCTs cannot correct the publication bias as the reviews are based only on the known and the not discontinued RCTs. The Legislator’s parry was then to force industrialists to make public all the RCTs they were setting up with the details of their main features, notably the dates of initiation and termination, including any discontinued RCT^{16b,17b,18b,19b,20b}. These *New Regulations* were far from being perfect but they had the merit of making investigators more cautious^{20c}. On the other hand, by doing so, the Health Authorities implicitly admitted that previous drug assessment procedures were not satisfactory. This should prompt us to re-assess all RCTs published before 2005, and to ask: what is the scientific value of

statin RCTs published before the *New Regulations*?

The logical corollary is to ask whether implementing these *New Regulations* resulted in any changes in the results provided by the statin RCTs. In other words, are those published after 2005-2006 different from those published before 2005?

The statin efficacy data

Post-2005 statin RCTs

As most statins were tested and marketed before the implementation of the 2005 (stricter) *New Regulations*^{16c,17c,18c,19c,20d}, how can we accurately evaluate today the real effects (both safety and efficacy) of the statins?

A first step is to compare the clinical effects of the “ancient” and “young” statins. The RCTs testing the “young” statins were conducted and/or published after 2005-2006. If the new RCT data (efficacy and safety) testing the “young” statins are in agreement with those published before the implementation of the *New Regulations* (before 2005-2006), this would be extremely reassuring regarding the real effects of the “ancient” statins and the robustness of the “ancient” RCT results.

The only statin that has been tested (against placebo) after the implementation of the *New Regulations* is rosuvastatin. Whether rosuvastatin may reduce cardiovascular complications was tested in four RCTs:

- The JUPITER trial where the patients were apparently free from cardiovascular disease and carried a rather moderate risk of cardiac death^{21a};
- The CORONA trial where patients were all survivors of a prior acute myocardial infarction (AMI) – with various degrees of cardiac dysfunction – and at a quite high risk of AMI recurrence and cardiac death^{22a};
- The GISSI-HF trial where all patients had cardiac dysfunction – 50% following a previous AMI, and 50% due to other heart disease – and a high risk of cardiac death^{23a};

- The AURORA trial where patients presented with severe renal failure, with 50% having already suffered an AMI or other ischemic complications. Evidently they had a major risk of recurrent AMI and cardiac death^{24a}.

Thus, a large proportion of the patients recruited in these 4 rosuvastatin RCTs were in the context of secondary prevention, thereby testing what appears as an indisputable statement, namely: *“beyond any doubt, statins are effective in secondary prevention”*^{25a,26a,27a,28a}.

A similar statement that is tested by these rosuvastatin RCT's is: *“the higher the risk of AMI, the more the reduction of cholesterol levels by means of a statin will be beneficial”*^{25b,26b,27b,28b}. The patients in AURORA – with the highest risk – should get the greatest benefit and those in JUPITER – with the smallest risk – the least benefit.

Let us start with the patients whose risk was the lowest.

The JUPITER trial

The JUPITER trial was a primary-prevention trial^{21b}. About eighteen thousand participants selected on the basis of a moderately elevated CRP (C-reactive protein) were distributed randomly into two groups: one was treated with a placebo, the other with rosuvastatin^{21c}. The primary hypothesis was to test rosuvastatin against placebo. However, it is likely that an implicit additional objective was to test whether CRP levels could serve as indicators for the prescription of a cholesterol-lowering drug, even in patients with normal or even low blood cholesterol levels. Indeed, knowing that the main investigator of JUPITER also held part of the licence for the CRP assay kit – the other owner being one of the major Boston hospitals – indicates that very serious conflicting interests were present^{21d,29a}.

One must remember that rosuvastatin, being the last statin arriving on the market, faced a major problem: the presence of the “ancient” statins, already considered as wonder-drugs. So, how could the pharma company lay its' hands on even a small part of the market, next to or against the competitors' statins?

The pharmaceutical industry does not like to compare face-to-face one drug to another for fear that the lack of significant difference between the two treatments might lead to the rejection of the new one. JUPITER was therefore supposed to demonstrate that rosuvastatin *is* indicated in a specific “new” category of patients, i.e. those with slightly raised CRP levels. JUPITER was a potentially win-win RCT: good for the CRP assay (and licence owners) and good for rosuvastatin and its’ producer^{20e,21e,29b,30a,31a}.

What happened with JUPITER? The whole story has been told in several articles and book chapters^{20f,21f,29c,30b,31b}. To put it short, by the end of 2007, the investigators and the sponsor announced highly favorable results for rosuvastatin and that the trial should be discontinued^{30c,31c}. According to them, it would have been unethical to leave millions of potential patients without treatment when they had already demonstrated the highly significant protective effect of rosuvastatin, notably on cardiovascular mortality^{20g,21g,29d,30d,31d}. Accordingly, in March 2008, a press release announced the discontinuation of the JUPITER trial, with an average follow-up of less than 2 years per patient^{29e,30e,31e}. The adequacy of this premature discontinuation was widely challenged^{20h,21h,29f,30f,31f}; but the investigators and the sponsor answered that the discontinuation process was scientifically validated, and ultimately decided by a committee supposedly “independent from the sponsor”. However, this committee had strong ties (in general) to the pharmaceutical industry^{20i,21i,29g,30g,31g}. In November 2008, the results of JUPITER were published^{21j} and controversy grew further as many realised that the mortality data were not presented correctly. Criticisms abounded, and so did the answers and counter-attacks of the investigators^{20j,21k,29h,30h,31h}. As the debate progressed, new data (previously concealed) were reported by the investigators or the sponsor, accompanied by rather surprising, not to say unacceptable, modifications in the survival curves^{29i,30i,31i}. This definitely raised suspicion of major flaws and possibly of misconduct in the way JUPITER was conducted and reported^{20k,21l,29j,30j,31j}. For instance, at least five different versions of cardiovascular mortality data were reported^{31k}, which obviously is unacceptable^{29k,30k,31l}. Cardiovascular mortality was ultimately not judged different in the placebo and rosuvastatin groups and the small difference in

overall mortality was not validated by the statisticians of the FDA^{29l,30l,31m}. As the raw clinical data, detained by the sponsor, are not available to independent experts and have not been examined by the FDA experts, it remains however impossible to make any definite conclusion regarding the true effectiveness of rosuvastatin in JUPITER. Admittedly, the lack of effect on death rate and the existence of mortality data tampering, do not by itself call into question the effectiveness of rosuvastatin against non-lethal complications. After all, if that medicine does not lengthen survival, it could improve quality of life by reducing nonfatal cardiac complication rate. The answer was indirectly given by the three other trials testing rosuvastatin – CORONA, GISSI-HF, AURORA – which did not report any effect on non-lethal complications^{22b,23b,24b}.

Was the premature discontinuation of JUPITER a deliberate form of tampering? Surely, the investigators must have known that they would be criticized for this, as many scientists consider that when RCTs are stopped early for benefit, they usually show implausibly large treatment effects and that their findings should therefore be seen with scepticism^{32a,33a}. So what could have been the true reason for this methodological flaw in JUPITER? The answer might lie with the unexpected significant increase of new cases of diabetes in the rosuvastatin-treated patients. The investigators tried to minimize this finding in their first report in 2008^{21m} and in subsequent analyses of their data, claiming that “*the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard*”³⁴. They wrongly seem to support the idea that the only consequences of diabetes are cardiovascular complications, forgetting that type-2 diabetes increases risk of many non-cardiovascular diseases such as cancers, eye and kidney diseases, dementia and cognitive decline, depression and bone damage among many others^{35a,36a,37a,38a,39a,40a}.

This statin-diabetes issue is further discussed below in the *safety* section.

Other rosuvastatin trials: CORONA and GISSI-HF

Let us start with the CORONA trial which was the first RCT to rationally test a statin in patients with chronic heart failure. It was published in 2007^{22c}. Over 5,000 AMI survivors aged 60 or more were randomised to

receive either a placebo or rosuvastatin. Despite a striking reduction in blood cholesterol level, patients taking rosuvastatin had no clinical benefit whatsoever, particularly in terms of survival. The occurrences of cardiac death, AMI and other non-lethal ischemic complications were unambiguously similar in the two groups, indicating that in secondary prevention of AMI cholesterol-lowering with rosuvastatin does not result in any protection.

This came in complete opposition to previous post-hoc analyses of RCTs and also meta-analyses,^{41a,42a,43a} all claiming that statins have beneficial effects on several endpoints, including mortality and non-lethal complications, in patients with cardiac dysfunction and chronic heart failure, with or without coronary heart disease. One of the major lessons of CORONA therefore was to confirm that only RCTs testing clearly defined primary hypotheses – and only a primary hypothesis^{4c,7b,8b,20l} – can provide a reliable evaluation of the efficacy of any medicine.

In other words, the well-spread theory, based on ancient RCTs, that statins are unambiguously protective in secondary prevention should be rediscussed in light of more robust data provided by more recent and more credible RCTs, such as CORONA.

But then, how can we explain the discrepancy between CORONA and “ancient” RCTs testing a statin in secondary prevention – such as 4S^{44a} for instance – as explaining discrepant *scientific* data is a fundamental work of independent scientists?

Some have curiously said that the failure of CORONA to show any benefit of rosuvastatin was hardly surprising since there was no reason for the statin to protect elderly heart-failure patients. According to these post-hoc claims, the statin was supposed to prevent ischemic heart attacks, certainly not to extend the life of elderly patients with ruined hearts by stopping the progression of cardiac dysfunction. The analysis of CORONA outcomes shows that this argument is not valid: most deaths occurred during a recurrent AMI, and only a minority because of progression of heart failure^{22d}. This is no surprise as previous studies have shown that recurrent AMI is the first cause of death following a prior AMI with cardiac dysfunction⁴⁵; and this argument – the efficacy of statin to prevent AMI – was the true reason to conduct CORONA specifically in post-AMI

patients^{22e}. Finally, when the authors analysed their results, there was no difference when comparing patients according to age or to degree of cardiac dysfunction at baseline: the youngest did not benefit any more than the oldest, and those who suffered from minor or no symptoms of heart dysfunction were no more protected than the most severe cases^{22f}.

Clearly, CORONA came as an unexpected blow for the sponsor and for all those claiming that statins are effective in secondary prevention of AMI. This was reinforced when Italian investigators reported the results of the GISSI-HF trial where approximately 50% of the patients recruited had very similar characteristics to the CORONA population (except that they were younger) and where again no benefit was demonstrated in the rosuvastatin group^{23c}.

It is pointless to discuss the GISSI-HF results in detail, although it was a remarkable piece of clinical research. All one needs to say is that, like CORONA, GISSI-HF failed to show any benefit of cholesterol-lowering with a statin in secondary prevention. Furthermore, as the results of CORONA and GISSI-HF were known by the sponsors and most statin experts before the results of JUPITER were revealed, there was no doubt as to the crucial importance for the rosuvastatin sponsor of salvaging JUPITER (and rosuvastatin) whatever the methods (including premature termination), so as to convince the sceptics.

The AURORA trial in chronic kidney disease

In the AURORA trial, rosuvastatin was tested against placebo in patients with severe chronic kidney disease, some of them with a previous AMI or other cardiac ischemic syndromes, thus again in secondary prevention^{24c}.

Renal failure patients being at high risk of AMI, the expected benefit from lowering their cholesterol level has also been considered as very high. Indeed, for years, on the basis of meta-analyses using weak data extracted from studies not designed to primarily test the effectiveness of statins on renal failure patients⁴⁶, these patients (and their doctors) were misled into believing that their cholesterol level should be lowered as much as possible^{20m}.

So what did AURORA show? The results were the same as in

CORONA: no clinical benefit at all – for both fatal and nonfatal complications – despite a striking reduction in blood cholesterol^{24d}.

AURORA ended the fable that cholesterol-lowering by a statin is useful in chronic renal failure. Actually, AURORA confirmed the negative results of a previous RCT named 4D,^{47a} discussed below in the statin-diabetes section, that had tested the effects of atorvastatin in similar kidney failure patients. Thus, AURORA and 4D again confirmed that we should not trust results of individual studies that do not respect the strict methods of RCTs based on a well-defined primary hypothesis^{7c,8c,20n}. Evidently the same goes for meta-analyses^{7d,8d,20o,25c,26c,27c,28c,32b,33b,41b,42b,43b,4d} in which such studies are included. Despite this evidence, investigators still recently published new meta-analyses mixing well-conducted RCTs (such as AURORA and 4D) with a myriad of commercial studies reporting secondary endpoints or post-hoc data^{48a,49a}, resulting in the curious claim that statins might be useful in chronic renal failure patients. The inadequacy of such methods is evidenced by the fact that the results differed. One study claimed that statins reduce the risk of cardiovascular complications in patients with chronic kidney disease, including those receiving dialysis^{48b} while another concluded that there was no effect in patients on dialysis^{49b}. One meta-analysis showed no effect of statins on stroke^{48c} while the other concluded that statins did reduce stroke in patients not on dialysis^{49c}. Such studies should be discarded.^{48d,49d}

Curiously, in the most recent RCT testing intense cholesterol-lowering (with simvastatin plus ezetimib) in patients with chronic kidney disease, the SHARP investigators concluded that reduction of cholesterol with such a strategy “*safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic disease*”, and in particular the effects were similar in patients on dialysis and those who were not^{50a}. In fact, in SHARP, there was no significant effect on coronary death, nonfatal AMI, any major coronary event and all-cause death. The significant effect on the composite endpoint called “total cardiovascular events” (619 events in the placebo group vs. 526 in the simvastatin plus ezetimib group) was almost totally the consequence of the between-group difference in the revascularisation procedures (352 vs. 284)^{50b}. As discussed earlier in that

review^{12b,13b} and elsewhere^{20p,30m,31n}, revascularisation is not a complication – but a medical decision which requires unblinding – and should be considered as very soft endpoint which cannot serve to judge the efficacy of any medicine against cardiovascular disease. In addition, the trial was criticized because of some uncertainty concerning the primary endpoint and a lack of clarity in the statistical analysis plan⁵¹.

Thus, there is no evidence behind the recommendations to lower cholesterol in chronic kidney patients. The whole story – including the “ancient” and recent RCTs – illustrates the weakness of the scientific reviewing process in medical journals and the persistence of significant links between some “experts” and commercial interests.

Summary on recent statin RCTs

A first conclusion is inevitable: taken as a whole, the 4 RCTs testing rosuvastatin – all conducted or published after the implementation of the 2005 *New Regulations* – show that cholesterol-lowering with that specific statin is not proven to be effective, whether in primary or in secondary prevention. This is in total contradiction with most “ancient” commercial RCTs, all published before the *New Regulations*.

The next question is obvious: if rosuvastatin appears ineffective, what about the “ancient” statins, allegedly remarkably effective on clinical outcomes but less effective than rosuvastatin to lower cholesterol?

Pre-2005 RCTs: are “ancient” statins better than rosuvastatin?

ATORVASTATIN

As mentioned above, statin investigators and industrials do not favour comparing two statins face-to face. Indeed, if comparative studies fail to detect any difference, it would mean that the “new” statin is no better than the old. But then, if the new statin is proven ineffective it would imply that the ancient one is also ineffective. This would be another indirect manner of demonstrating that the “ancient” commercial RCTs truly were biased.

A recent study, conducted according to the *New Regulations*, compared rosuvastatin with atorvastatin, one of the “ancient” allegedly miraculous statins. The findings are quite interesting.

The SATURN trial, published in 2011, compared the effects of rosuvastatin to those of atorvastatin, in the absence of a control (placebo) group^{52a}. The primary end-point was progression of atherosclerotic plaque. They claimed that plaque volume – measured with sophisticated imaging techniques – is predictive of cardiovascular complications. The number of patients was relatively small (about one thousand), as well as the duration of the follow-up (two years). The results showed no significant difference between the two statins regarding the evolution of plaque volume during follow-up, which was curiously interpreted as showing that both statins were equally effective in slowing down the plaque evolution, when there was no control group^{52b}. In addition, there was no difference in the number of major cardiovascular complications: 49 vs. 52^{52c}. This is a critical point. One could argue that the trial was rather short and the number of patients too low to expect any significant difference to emerge between both groups. However, the total lack of difference (even no trend) after two years does not raise hope that, even with many more patients, atorvastatin would suddenly recover the miraculous effects it had boasted in the publications made before the stricter *New Regulations*.

Thus, according to SATURN, atorvastatin is no better than rosuvastatin and, as the latter is totally ineffective^{20q,21n,22g,23d,24e,29m,30n,31o}, so must be atorvastatin. This leads to the consideration that what caused the change of atorvastatin, going from a wonder-drug into an ineffective one, might be the implementation of the 2005 *New Regulations*^{16d,17d,18d,19d,20r}. We therefore chose to reconsider the results of another RCT testing atorvastatin in secondary prevention: the MIRACL trial published in 2001 and often presented as an unambiguous demonstration that atorvastatin is effective to prevent cardiovascular complications^{53a,54a}.

Why come back on MIRACL in 2015? The MIRACL trial is quite typical of the commercial RCTs undertaken long before the 2005 *New Regulations*. MIRACL compared atorvastatin (80 mg) to a placebo in over 3,000 patients who had just suffered an AMI, within 24 hours to 3 days after their admission to hospital. This was a quite perfect situation to assess the effectiveness of a statin in secondary prevention. The investigators wished to demonstrate that the effect of large doses of atorvastatin was close to immediate. Importantly, the trial was totally controlled by the

sponsor. Even the main statistician was a member of the sponsor staff^{53b}.

The results were unambiguous: there were 68 deaths in the placebo group, against 64 in the atorvastatin group; 113 non-lethal AMIs in the placebo group vs. 101 in the atorvastatin group; and 10 vs. 8 cardiac arrests, respectively^{53c}. The hypothesis that atorvastatin may protect from recurrence in secondary prevention should therefore be rejected without any hesitation. However, MIRACL was^{53d,54b} – and still today⁵⁵ is – presented as an unequivocal demonstration that a statin – in particular atorvastatin – should be imperatively prescribed in secondary prevention.

How did the investigators and the sponsor of MIRACL turn around the evidence? The procedure was subtle. They added a new clinical cardiac endpoint category, in place of AMI or unstable angina. In their own words, the new category was: “*recurrent symptomatic myocardial ischemia with objective evidence requiring emergency hospitalization*”^{53e}. These patients were not suffering AMI or unstable angina according to established criteria but of something else, i.e. *hospitalisation* – an endpoint still more soft than the *revascularisation* endpoint (discussed above) – which, in any case, can serve to judge the efficacy of a drug in scientific medicine. Moreover, the validation of that endpoint totally depended on the data collected by field investigators who belonged to the sponsor’s staff. By performing this curious validation-classification of a “new” endpoint, at last something appeared to be slightly different in the two groups: they recorded 130 and 95 of these types of “events” respectively in the placebo and atorvastatin groups. One might be tempted to smile if it were not so outrageous.

The failure of statins to reduce the risk of recurrence and death in the early high-risk period following AMI or acute coronary syndromes – the worst phase in secondary prevention – has been confirmed since then in various meta-analyses^{56,57} thereby also confirming that MIRACL was a flawed trial. The only conclusion then is that we do not have any evidence that rosuvastatin or atorvastatin (even at high dose) are effective in secondary prevention.

SIMVASTATIN

For years, millions of AMI survivors worldwide have been treated with simvastatin on the basis of a single trial, the 4S trial (*Scandinavian*

Simvastatin Survival Study), the findings of which were published in 1994 and were showing significant effects with reduction of both cardiac death and nonfatal complications^{44b}.

The 4S trial is the one and only published RCT assessing the effect of simvastatin in secondary prevention^{44c}. It is surprising that a world leader in the pharmaceutical industry set up only one trial to test such a promising drug. It is more likely that other RCTs were conducted, but that their results remained unpublished, probably because they were not as favourable as previously hoped. We would be facing again a “*publication bias*”^{3c,4e,5d,6c}.

The fact that the sponsor of 4S was the same company that marketed Vioxx is to be noted. And also that the trial was conducted on the field by the sponsor’s staff and that, as in MIRACL, the main statistician of the trial belonged to the sponsor’s staff^{44d} which would today be unacceptable. Nonetheless, given the ineffectiveness of atorvastatin in secondary prevention, is there any indication then that simvastatin is better than atorvastatin?

Simvastatin was compared to atorvastatin in a trial called IDEAL, published in 2005^{58a}, at a time when investigators and sponsors began to be very prudent, 2005 being right in the middle of the transition phase between the ancient and *New Regulations*. Briefly, in IDEAL, almost 9,000 patients with coronary heart disease were treated with either atorvastatin or simvastatin. The LDL cholesterol level was a bit lower in the atorvastatin group, but the 11% reduction in the primary endpoint (nonfatal AMI + cardiac death) in this group was not statistically significant^{58b}. More specifically, there was no difference between groups in total death rates (374 vs. 366) nor in cardiac deaths (178 vs. 175).

In our sense, IDEAL is therefore a good source of information as it shows that atorvastatin and simvastatin are similar in terms of clinical effectiveness over a period of nearly 5 years in secondary prevention^{58c}. As atorvastatin is apparently ineffective, simvastatin appears to be ineffective too. The 1994 “4S miracle”^{44e} was not reproduced. As discussed in the Introduction section, reproducibility of scientific data is the cornerstone of their credibility^{1c,2c}.

As long as we do not have access to the raw clinical data of 4S – and because the methods used in 4S are questionable (in particular, the lack of

independent statistical analyses) – it seems prudent to consider 4S as a doubtful RCT.

Is intensive lowering of cholesterol more effective?

It has been claimed that more versus less intense statin regimens is more effective to reduce cardiovascular complications⁵⁹. Is there any difference between the “ancient” and recent RCTs?

The SHARP trial, discussed above and testing intense cholesterol-lowering (with simvastatin plus ezetimib)^{50c} was a first answer: no significant effect of intense cholesterol-lowering.

In fact, only one RCT investigating intensive cholesterol-lowering with a statin has been published after the 2005-2006 transition period; it is the SEARCH trial comparing 80 mg versus 20 mg of simvastatin in a huge (n=12,064) population of AMI survivors^{60a}. Results after a mean follow-up of almost 7 years are by no way ambiguous: there was no significant difference between groups for any cardiovascular endpoint, including the very soft composite endpoint (p=0.10). More specifically, more intense simvastatin regimen did not significantly reduce coronary death (447 vs. 439), major coronary events (1189 vs. 1225), stroke (255 vs. 279) or any death rate (964 vs. 970)^{60b}. The only possible conclusion is that the tested hypothesis, i.e. intensive statin therapy is more effective, must be rejected. Neither the sample size nor the duration of follow-up could explain the failure. Curiously, the investigators concluded that the SEARCH results “*were consistent with previous RCTs*” demonstrating that more intense statin therapy safely produces extra benefits^{60c}. This is obviously wrong and once again raises concerns about the review process in medical journals.

Summary of the studies comparing statin vs. statin

In short, rosuvastatin (which is not effective) is not different from atorvastatin which, itself, is not different from simvastatin. This leads to the conclusion – based on the comparison of statin versus statin – that the “ancient” statins (simvastatin and atorvastatin) are not different from the youngest one (rosuvastatin). Thus, cholesterol-lowering with any of these

medicines yields no detectable benefit against cardiovascular disease, in particular cardiac death and nonfatal AMI, and no effect on overall survival.

This lack of difference between the “ancient” and young statins was recently, and indirectly, supported by a very large cohort study based on the huge French national health insurance database comparing the cardiac and cerebrovascular prognosis of 106,941 patients prescribed rosuvastatin with 56,860 patients prescribed simvastatin, the average follow-up being 36 months⁶¹. No difference between the two statins was observed in this *real-life* study, suggesting again that the lack of significant protective effect of rosuvastatin may represent the true effect of statins in general and, by extension, also of cholesterol-lowering against cardiovascular disease.

Furthermore, this is confirmed by the fact that apparently intensive statin regimen is no better than a less intensive one. Finally, the observed discrepancy between “ancient” and more recent RCTs testing the different statins implies that mixing data from these two categories of RCTs in meta-analyses should no longer be accepted.

On the contrary, to be credible, any new meta-analysis should separately analyse RCTs conducted before and after the implementation of the 2005 *New Regulations*; and should separately analyse the RCTs testing “ancient” and “young” statins.

In the same line of reasoning, *official* recommendations should be rewritten on the basis of these new systematic reviews and meta-analyses.

The noncardiovascular and safety statin data

Beyond the cardiovascular issue, statins have repeatedly been presented as medicines having “other” major health effects in relation or not with cholesterol-lowering. Some were potential benefits, others could be deleterious. There are many different aspects and all cannot be discussed in the present review. We have selected the thromboembolic and diabetes issues.

Here again, do the most recent studies, compared with the “ancient” ones, provide some new information about statins? In case of discrepancy between the “ancient” and recent noncardiovascular statin data, this would be another indication that “ancient” RCTs have been, intentionally or not, flawed.

Statins and thromboembolisms

As an example, let's return to the JUPITER trial^{21o}. Despite the premature termination of the trial and the fact that thromboembolism was not a primary endpoint – both considerably increasing the possibility of a chance effect and biased results – JUPITER investigators nonetheless claimed that rosuvastatin significantly reduces the occurrence of symptomatic venous thromboembolism⁶². In a subsequent meta-analysis⁶³ published in 2012 which analyzed published and unpublished results of statin RCTs – including JUPITER – investigators found that statins do not significantly reduce the risk of venous thromboembolism: events occurred in 0.9% of the participants who were given statins and in 1% of the participants who were given placebo. The whole issue strongly indicates (as expected) that JUPITER results about venous thromboembolism happened by chance. Until we get new and consistent data, the theory that statins may have some anticoagulant properties should be rejected. The thromboembolism/JUPITER story is another illustration that JUPITER is a flawed RCT.

Statins and new-onset diabetes

Whether statins induces new-onset diabetes is a major question because diabetes is a serious disease with many complications including indeed AMI and stroke on one side but also renal and ophthalmic diseases, cancers, depression, cognitive decline, dementia and some others^{35b,36b,37b,38b,39b,40b}. Thus, if statins actually induce new-onset diabetes, it is clearly a relevant issue.

In fact, they do. Curiously it is only with the JUPITER trial in 2008 that the statin-diabetes issue was revealed^{21p} and, as discussed above, it has likely been the main reason to prematurely stop JUPITER. It took 4 additional years before the FDA sent out a warning concerning this undesirable side effect, stating that statins definitely increase the risk of de novo diabetes⁶⁴.

This means that it took at least 30 statin RCTs and 30 years – during which the statins were fully prescribed – to bring to light this toxic effect. Is it possible that during such a long period of time, investigators (and their

sponsors) had seen nothing? The statin-diabetes story is a remarkable illustration of high bias in reporting of harmful outcomes within studies, including sponsored RCTs^{65,66}. In fact, statins not only increase the risk of *de novo* diabetes, but even more frequently increase insulin resistance and metabolic syndrome, probably through their effect (at least in part) on skeletal muscles⁶⁷.

Nevertheless, the investigators who had seen (or reported) nothing until then, immediately reacted by claiming that we must not change anything in the way of prescribing statins^{68a,69a,70a}: their “reasoning” was (and still is) that as statins are highly effective in preventing AMI and stroke in diabetics, becoming a diabetic is not a problem as the patient would ultimately anyway be protected from cardiovascular problems^{68b,69b,70b}.

Probably untrue^{71a,72a}, this reasoning does in addition not take into consideration the previously mentioned several complications of diabetes that statins cannot reduce or may even stimulate^{20s,30o,31p,35c,36c,37c,38c,39c,40c,73a,74a,75a,76a,77a,78a,79a,80a}. And we must remember that most patients prescribed a statin are at low risk of AMI or stroke. Even if statins were really protective – an elusive theory – only a very small proportion of the treated patients would benefit. On the other hand, among the huge number of low-risk patients treated with statins, a significant proportion (see below) can become diabetic (or insulin-resistant) and suffer complications from this – including non-cardiovascular complications – in addition to the other deleterious side-effects of statins^{73b,74b,75b,76b,77b,78b,79b,80b,81,82,83,84,85} which have been systematically underestimated in the “ancient” statin RCTs and meta-analyses^{86,87,88,89}. This is in total contradiction with fundamental medical ethics stating: “*Primum non nocere, deinde curare*” [i.e. “First do no harm, then cure”].

Risk of inducing diabetes

Because of the lack of credible information about statin safety from commercial statin RCTs –well confirmed by the fact that the diabetes-statin relation was only very recently revealed – it is difficult to know the exact prevalence of this side-effect. Taking things prudently, the pro-diabetic effect of statins could be far from negligible in clinical practice. In

a real-world setting, the risk of new-onset diabetes has been reported to increase with dose regimen and as adherence with statin treatment increases; the relative risk of new-onset diabetes may reach 40 to 70% in a real-world setting^{90,91,92}. In brief, statins could induce roughly one *de novo* diabetes for every 100 to 150 patients taking an average dose. Things would be much worse with the very large doses currently recommended. In France, for instance, this means that every year at least 47,000 *de novo* diabetes cases could result from the current treatment of roughly 7 million patients^{20t,30p,71b}. These figures are probably underestimated, considering the difficulty that exists to get reliable figures.

Do statins prevent cardiovascular complications in diabetics?

Let us first cautiously have a look at the existing data as many experts are claiming that statins do prevent cardiovascular complications in diabetics^{68c,69c,70c} whereas others say the opposite^{71c,72b}. To stay in line, only robust data should be retained.

How many RCTs have tested the effects of statins in diabetics as a primary hypothesis? There are three, namely CARDS^{93a}, ASPEN^{94a} and 4D^{47b} all three conducted and published before the 2005 *New Regulations*^{16e,17e,18e,19e,20u}. Despite the fact that these three RCTs did not show unambiguous benefits of statins in diabetics, investigators claimed the opposite. So, let us carefully examine the data.

In brief, 4D is a RCT testing atorvastatin against placebo (median follow-up 4 years) in 1255 diabetics receiving maintenance haemodialysis^{47c}. There was no significant difference between the 2 groups for the primary endpoint (relative risk 0.92) and for total mortality (relative risk 0.93). The risk of fatal stroke was significantly increased among patients receiving atorvastatin (relative risk 2.03). The only possible conclusion should have been that the statin did not protect diabetics^{47d}. The investigators actually concluded that “*initiation of statin therapy in patients with diabetes who already have end-stage renal disease may come too late to translate into consistent improvement of the cardiovascular outcome*”^{47e}. In a subsequent substudy of 4D however – reanalysing the dataset and making an *a posteriori* subgroup analysis, thereby drastically increasing a chance effect

– they claimed that “*in patients with type 2 diabetes mellitus undergoing haemodialysis, atorvastatin significantly reduces the risk of fatal and nonfatal cardiac events and death from any cause if pre-treatment LDL-cholesterol is >145 mg/dl*”⁹⁵. This is simply not acceptable and again raises questions about the reviewing process in some medical journals.

The failure of 4D to show a protective effect of atorvastatin is supported by the results of another RCT in patients with haemodialysis, the AURORA trial^{24f} discussed above, in which rosuvastatin also failed to protect against cardiovascular complications. Nonetheless, the question raised by the 4D investigators in their first original report^{47f} – lack of benefit because of a too late initiation of treatment – might be relevant. It has been examined in ASPEN, a RCT where diabetics with severe renal dysfunction were excluded^{94b}.

The ASPEN trial investigated the cardiovascular effects of atorvastatin in diabetics, with or without documented coronary heart disease (CHD)^{94c}. The trial was originally designed as a secondary prevention trial, but updates in treatment guidelines for individuals with CHD impaired recruitment. The protocol was therefore amended to enrol subjects without prior CHD^{94d}. Following the new statistical calculations, the trial was powered to detect differences between the statin and placebo groups but not to detect differences in the primary or secondary prevention subgroups alone^{71d}. Subjects were followed up during 4 years. There was no significant difference between groups for the primary endpoint (166 and 180 events for the atorvastatin and the placebo group respectively), for cardiovascular mortality (38 and 37 deaths) and overall mortality (70 and 69 deaths). Thus, the results of ASPEN were similar to those of 4D, but in the absence of severe renal dysfunction. The extension of criteria for enrolment was likely not an important cause of bias since the statistical protocol was amended accordingly. The two trials complement each other: in 4D (diabetics with severe renal dysfunction), patients were at very high risk while in ASPEN patients were at rather low risk.

In CARDS, the third RCT testing atorvastatin against placebo, 2838 diabetic patients were included^{93b}. In contrast to ASPEN and 4D, significant reduction of a composite primary endpoint was reported (relative risk 0.63). However, the numbers of primary endpoints in CARDS were

small (83 and 127 in the statin and placebo group) despite the fact that the investigators used a *composite* primary endpoint mixing hard and soft (such as revascularisation) events. This criticized strategy considerably increases the probability of a chance effect^{12c}. Indeed, there was no statistically significant difference for all-cause mortality and coronary mortality. In this context, the decision of early termination – two years before the anticipated end without a clear justification – was inadequate. Furthermore, the clinical inconsistencies seen in CARDS suggest that the validation and classification of the endpoints were questionable. In addition – because, as written by the investigators, “*site monitoring, data collection, and data entry was done by sponsor’s staff*”^{93c} – the possibility of outcome reporting bias in CARDS must be considered. Whatsoever, it was ethically and scientifically indicated to continue the trial to definitely clarify the effect on cardiac and total mortality. The CARDS trial has to be suspected of being biased until confirmed by other trials. No such confirmation has occurred. On the contrary, both 4D and ASPEN failed to report any benefit (not even a trend toward benefit) of atorvastatin in diabetics^{47g,94e}.

Taken together, the three RCTs testing a statin in diabetics as a primary hypothesis failed to show any benefit. This was confirmed in the ACCORD trial⁹⁶ where aggressive cholesterol-lowering did also not yield any benefit in diabetics.

Summary of the statin-diabetes issue

Despite the absence of evidence, why do the “official” recommendations still state that most diabetics (if not all) should be treated with cholesterol-lowering drug^{97,98}?

One explanation is that these recommendations are usually based on meta-analyses which are supposed to objectively synthesize the whole scientific knowledge about the issue. In fact, even meta-analyses examining whether statins may protect diabetics do not all show the same results. For instance, Chang et al concluded in 2013 that no significant benefit of statin is found in primary ($p=0.24$) as well as in secondary ($p=0.26$) prevention of cardiovascular complications in diabetics^{72c} whereas the Cholesterol Treatment Trialists’ Collaborators (CTTC) concluded in 2008 that statins

reduce the risk of AMI in diabetics, even stating that statin should be considered for all diabetics^{99a}. How can we explain such discordant conclusions?

The CTTC meta-analysis pooled the data from 14 statin RCTs but none of the statin RCTs published after 2005 was included thereby curiously excluding 4D^{47h} and ASPEN^{94f}. Moreover, among the 14 included RCTs, only one – CARDS^{93d} for which we have exposed the major methodological problems – prospectively randomized diabetic patients and thus actually tested the effect of a statin in diabetics as a primary hypothesis. Data from the other 13 trials were from nonrandomized subgroups of diabetics – representing between 1% and 35% of the total of the patients enrolled in each trial^{99b} – and therefore open to major bias. Even more surprisingly, 4D and ASPEN – although not included in the main analysis – were mentioned at the end of the discussion section of the CTTC report, the authors writing that “*their conclusions are not materially affected by the results of ASPEN and 4D trials*”^{99c}. On the contrary, true science imposes to only consider statin RCTs where diabetics were prospectively randomized – namely CARDS, 4D and ASPEN – as Chang et al did^{72d}, rather than partial retrospective data from nonrandomized subgroups of diabetics. The CTTC meta-analysis is therefore flawed by a major selection bias^{99d}. Consequently, the only possible interpretation based on robust data is that statins do not protect the diabetics.

The conclusion is therefore that on the basis of the most recent statin RCTs discussed here, there is no evidence that statins reduce the risk of cardiovascular disease in diabetics while there is on the other side no question about their diabetogenic effect and other deleterious side-effects.

It is high time to re-assess the whole statins-diabetes issue.

In summary, we propose 9 key issues that put into question the scientific basis justifying the use of statins:

1. Obvious discrepancy between “ancient” – before the 2005 *New Regulations of clinical trials* – and more recent statin trials in terms of both efficacy and safety.
2. In the recent trials, rosuvastatin was not effective in secondary

prevention and most probably not in primary prevention.

3. No statin has proven to be superior to rosuvastatin. Statins can therefore all be considered as ineffective.
4. Recent trials clearly indicate that intense cholesterol-lowering does not protect high-risk patients any better than less intense statin regimens, confirming that the cholesterol theory saying that “*lower is better*” is wrong.
5. More specifically, in view of the lack of evidence, cholesterol-lowering and statins are useless in chronic heart failure, chronic kidney failure and diabetic patients.
6. In primary prevention, the data showing a protective effect of statins have a high likelihood of having been tampered with.
7. Most patients prescribed a statin at present are at low risk of stroke and AMI and the expected cardiovascular benefits can at best only be very small.
8. It took 30 years to bring to light the effect of statins on new-onset diabetes. This illustrates a high level of bias in reporting harmful outcomes in commercial trials.
9. Among the dozens of millions taking a statin, a significant proportion could become diabetic and get the many complications of diabetes, in addition to the many other adverse side-effects of statins.

Because of the above, a complete reassessment of statin therapy is mandatory.

Conclusions

A careful examination of the most recent statin RCTs and comparing them with “ancient” RCTs, as done in the present review, clearly shows that collectively and for years we have been very wrong regarding the health benefits (and safety) of statins.

We are entering a new era where full access to raw data from industry-

sponsored RCTs^{100,101} is the only way to permit transparency and to restore the credibility of clinical research. It is time to implement completely reliable methods to conduct medical trials so as to restore mutual confidence between all participants in the patient's care^{102a,103a,104}.

If the 2005 *New Regulations* definitely represented a step in the right direction^{16f,17f,18f,19f,20v}, it remains that investigators and industrials could still succeed in finding a way around them. Indeed, since 2006, the media in various countries report problems every week between the pharmaceutical industry (or the experts working with it) and the law courts^{105,106,107,108}.

So despite advances in clinical research and RCT transparency, there are still scientists and regulators – of the EMA for instance¹⁰⁹ – saying that the present regulations are not sufficient and should be reinforced¹¹⁰. Obviously, full access to RCT data (still not possible) would allow independent researchers to examine the risks and benefits of medicines and thereby counterbalance the industry's power to assess its own products in the “industry-sponsored” RCTs. Clearly, legitimate interests in the protection of private (industry) investments must be weighed against other legitimate interests, such as the benefit and the protection of patients. The right balance between these interests is an obvious duty for all stakeholders involved, including regulators. And truly, when industry investments have been paid back, years after publication of RCTs that justified the marketing of a new medicine, there is no reason remaining not to give free access to RCT raw data unless, of course, that there are things which are not to be shown...

We strongly call for an end to the dogmas about statin efficacy and safety, based on unrealistic clinical reports and flawed meta-analyses, leading to biased recommendations about statin use^{102b,103b,111,112} and ultimately extravagant situations and claims^{113,114}.

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Chapter Sixteen

Why Reported Statin Side Effects Are Just the Tip of a Titanic Iceberg

Duane Graveline, MD, MPH, Paul J. Rosch, MD

Editor's Note: The majority of this chapter is written in the first person since it is Dr. Graveline's compelling account of his personal experience with statins and his crusade to alert others to their sinister adverse side effects.

Abstract

I introduce the reader to an account of my two personal experiences of statin associated transient global amnesia (TGA) which led me out of retirement to a full time study of statin drug side effects. The fortuitous publication of my TGA story in the widely syndicated Peoples Pharmacy column resulted in a veritable flood of emails from statin damaged people permitting the recognition of the full scope of statin adverse effects long before Medwatch became functional in this respect. People were reporting many different forms of cognitive dysfunction, behavioral disorders, peripheral neuropathy, ALS-like disorders and rhabdomyolysis. Gradually the two faces of statins became evident. As mevalonate pathway inhibitors they block cholesterol synthesis while at the same time blocking CoQ10 and dolichols (the cause of most of our side effects) while the other face of statins inhibits nuclear factor kappa B creating both anti-inflammatory and immunomodulatory properties accounting for reduction of cardiovascular risk.

Introduction

Statins have become the most profitable and popular prescription drugs ever because of their efficacy in lowering cholesterol and LDL. The importance

of this stems from the lipid hypothesis, which postulates that lowering elevated cholesterol will significantly reduce coronary morbidity and mortality. This is based on studies done 100 years ago showing that experimental animals on a high cholesterol diet developed fatty deposits similar to those found in human atherosclerotic plaque. A half-century later, epidemiologic studies in different populations showed a very close correlation between saturated fat consumption, cholesterol levels and coronary disease deaths^{1,2}. The Framingham study³ also established cholesterol as a risk factor for heart disease. However, these were observational studies with serious flaws, and only an experiment that demonstrates the benefit of an intervention can prove a cause-effect relationship. In that regard, attempts to reduce coronary disease by restricting saturated fat to lower cholesterol failed, and some reported an increase in deaths.

The NIH sponsored Coronary Primary Prevention Trial was widely hailed as proof of the lipid hypothesis since it showed that cholestyramine, a foul tasting bile binding resin, lowered LDL and cholesterol and reduced coronary events in a synchronized fashion. However, this was of little practical value because of side effects and poor adherence^{4,5}.

While statins subsequently seemed to avoid these drawbacks, there is no proof that they are effective in primary prevention⁶. In addition, any benefits in coronary disease patients have now been shown to be due to pleiotropic effects such as reducing inflammation and clotting tendencies rather than lipid lowering⁷. As will also be demonstrated, there are growing and serious concerns about statin safety and how it is reported^{8,9,10a,11}.

How Were Statins Discovered And Why Do They Lower Cholesterol?

Statins were discovered in the early 1970's by Akira Endo, a Japanese biochemist, who hypothesized that penicillin and other chemicals in fungi killed bacteria by inhibiting their ability to synthesize cholesterol. After testing several thousand fungal extracts, he isolated three from a Penicillin mold, one of which, mevastatin, was the first statin¹². Mevinolin (MK-803), the first commercial statin, was subsequently isolated from an *Aspergillus* mold by Alfred Alberts and co-workers at Merck¹³, and received FDA

approval as lovastatin in 1987. Mevastatin, also known as compactin, was never approved, but pravastatin, a derivative, was discovered by Japanese scientists in 1979 and was approved there in 1989 and by the FDA in 1991. While developing lovastatin, Merck chemists also derived MK-733; a more potent cholesterol-lowering agent that was later named simvastatin. Simvastatin was approved in Sweden in 1988 and became available in the U.S. in 1991.

Cholesterol biosynthesis is a complex process involving over 30 enzymes and coenzyme Q10. The designation statin is used to describe products that interfere with this by inhibiting the HMG-CoA reductase enzyme. As this is one of the very early steps in the creation of cholesterol in the liver, statins also block the mevalonate pathway and the production of ubiquinone (Coenzyme Q10) and dolichols, which can have dire consequences. Cholesterol is made by most mammalian cells because it is a crucial component of cell membranes, and statins can disrupt this process as well.

All Statins Are Not Created Equal

There are two subtypes of statins: those that are natural and fermentation derived, such as lovastatin (Mevacor), pravastatin (Pravachol) and simvastatin (Zocor), and others that are synthetic; atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), rosuvastatin (Crestor) and pitavastatin (Livalo). The chemical structures of the three natural statins are very similar since they have a common source. Synthetic statins bear no resemblance to this configuration and differ from them with respect to cholesterol lowering properties. Rosuvastatin, atorvastatin and pitavastatin appear to be the most potent, with fluvastatin being the least. However, this rating may not apply to their ability to affect low and high density lipoproteins, apolipoprotein B, or triglycerides, which are also believed to influence risk for coronary heart disease.

Statins are often classified with respect to their solubility in fat (lipophilic) and water (hydrophilic). Atorvastatin, lovastatin, and simvastatin are lipophilic, whereas pravastatin, rosuvastatin, and fluvastatin tend to be more hydrophilic. Lipophilic statins cross the blood-brain barrier more readily, which could increase the likelihood of central nervous system complaints such as cognitive disturbances, memory loss and insomnia.

Statins also differ with respect to the frequency and nature of other adverse side effects that might be influenced by their lipophilic status. These include diabetes, congestive failure, neuropathy, certain cancers and rhabdomyolysis, a severe type of muscle disease. Cerivastatin (Baycol) was withdrawn because it caused rhabdomyolysis 10 to 80 times more often than other statins and was associated with over 100 deaths.

Statin interaction with other drugs can also vary considerably. Rhabdomyolysis is more frequent in patients when they are taking other drugs that increase statin blood levels. In one study, patients who took both verapamil (Calan, Verelan, Isoptin), and simvastatin (Zocor), experienced myopathy 10 times more frequently than patients who received simvastatin alone¹⁴. Pravastatin (Pravachol) and rosuvastatin (Crestor) levels are less likely to be elevated by other drugs because liver enzymes that eliminate them are not affected by medications that block the enzymes responsible for removing other statins.

The Reality of Statin Adverse Drug Reactions

Tens of thousands of statin users have complained to their doctors of weakness, instability, easy fatigue, muscle aches and pains, burning of their extremities, depression, personality change and faulty memory, to which their doctors generally have responded, “You have to expect this now. You are over fifty” or even, “statins do not do that.”¹⁵

Although these experienced doctors all have pointed to a reasonable presumptive diagnosis, few have been entirely comfortable with this explanation because of a curious recurring pattern in their presentation. All of these patients have been on statins of one brand or another and the transition from midlife vigor to the multiple infirmities of the elderly has been much too swift in most. In the few months since the previous office visit, an aura of senescence has evolved in these patients. Doctors deal with the passage of time on a daily basis and are acutely sensitive to its telltale first traces. The complaints their patients are reporting may be common even routine in the elderly yet these people are for the most part in their sixties and seventies and sometimes even much younger!

If anything out of the ordinary can be attached to these complaints of faulty memory, weakness and various aches and pains, it is their prematurity -

premature aging. Conditions are being complained about that ordinarily would not be seen until much later in life. Are these statin users being robbed of their “golden years”? Is it possible that their passage to senescence has been expedited? If so, what could be the mechanism?¹⁶

This series will take you on a journey where many doctors really do not want to go - not after decades of use of reductase inhibitor (statin) class of drugs. What doctor wants to admit that he or she has been wrong about the side effects of statin drugs that now appears to be much more important than originally thought?

I have been there, and I have done that, and it has not been easy. The very idea that my practice philosophy was wrong for many years is a bitter pill for me to accept and to think I was following the dictates of national leadership, marching in lockstep with everyone else to the misguided fallacy of cholesterol causation of arterial damage.

Those were the days when we doctors were delighted to have statins. After almost 40 years of treating cholesterol with ineffective medicines we finally had a drug that really worked. Cholesterol dropping 40 points in just a few weeks was a whole new world for us. And hardly a word about side effects. We were advised to look out for liver damage by doing a blood test after a few weeks and told to expect a few muscle problems in under 2% of our patients for which we needed only to drop the dose a bit.

Many physicians have doubted the hypothesis of cholesterol causation from the very beginning^{17a}. Gradually, very serious reports of adverse reactions started to come in along with surprising reports of studies showing benefit of statin use even when the cholesterol remained unchanged. Strangely, we observed that in almost half of the new heart attacks being reported the cholesterol levels were normal. Then reports began to accumulate of transient global amnesia, permanent myopathy, diabetes, permanent neuropathy, rhabdomyolysis, ALS and serious neuro-degenerative conditions.

Evidence of another effect of statins, independent of cholesterol, began to accumulate. The study that made a huge difference for me was a study called JUPITER¹⁸. This study selected men and women who ordinarily would not have been a candidate for statins with cholesterol levels all less than 130 and no significant CV risk but whose inflammatory marker,

(hs)CRP, was elevated. Half of these were given a statin, the other half took a placebo. After 19 months the ethics committee forced the stopping of the study because of excess heart attacks and stroke in the placebo group. It was deemed unethical to proceed.

Naturally there was a furor of controversy about these findings and it was in anticipation of this controversy that the study had been specially crafted yet two very important things emerged from this study: one was that cholesterol level appeared to have no relationship with cardiovascular disease risk and the second was that statins did work to lower this risk level as measured by this new inflammatory marker. Doctors have been reluctant to accept this because they had accepted cholesterol causality for well over 4 decades. Drug companies had only to shift marketing gears a bit to overcome this new reality for statins had been proving to be powerful anti-inflammatory agents in addition to an inhibitor of cholesterol synthesis for which they originally were designed.

So now we have a statin drug designed to be a reductase inhibitor that suddenly turns out also to have anti-inflammatory and immuno-modulatory properties and it is this added feature of the drug that gives the benefit¹⁹. The reductase inhibitor function blocks the the reductase step in the mevalonate pathway which synthesizes cholesterol along with CoQ10 and dolichols. The other new function is based upon the blocking of an intracellular transcriptase known as nuclear factor kappa B (NF-kB)²⁰.

So where are we? Statins now block cholesterol, perhaps the most important biochemical in the body, especially vital for the cognitive function of the brain and statins also block CoQ10^{21a,22a} and dolichols, critical to mitochondrial function and responsible for almost all of the side effects. Additionally, statins block NF-kB giving a modest anti-inflammatory benefit to high risk heart patients but decreasing our immune status, raising the specter of increasing cancer risk. The fact that this vital information was not revealed until more than a decade after statins were marketed proves that statins were marketed long before they were fully understood²³.

Cognitive Effects of Statins

With our statin drug experience of the past decade we have come to expect side effects such as liver damage, muscle pain and nerve damage. But the ever-increasing cognitive side effects from statin drugs are new and completely unexpected by both patient and physician. They strike at who we are, our very essence, for without our memory what are we?

Transient global amnesia strikes without warning²⁴, abruptly depriving one of the ability to formulate new memories. With no record of the past, every new face, thought, conversation or scene is a unique moment, a novel experience transiently entering a mind suddenly emptied of the past. Think of the utter horror of this instant depersonalization, the anxiety, the frustration, the constant query, “What has happened to me?”

Think of the concern of family and friends when their loved one has abruptly become a querulous being who can walk and talk but who has suddenly been transformed into a bewildered creature without memory or ability to converse, pathetically trying to cope with its strange new world.

Prior to 2000 transient global amnesia (TGA) was very rare^{25a}, almost a medical curiosity, and deserving of only a very limited description in most neurology textbooks. My medical community knew nothing of this.

In 1999 NASA (astronaut status) had called me in for my annual physical and because of modestly elevated cholesterol (270) placed me on Lipitor 10 mg. My first TGA occurred some 6 weeks later at which time my cholesterol was 155. This episode lasted 6 hours before I came to my senses in the office of the neurologist. The neurological examination was completely normal except for the amnesia. An MRI was ordered and the neurologist made a tentative diagnosis of transient global amnesia, cause unknown. I had been on Lipitor 10 mg for six weeks at this time.

I stopped the Lipitor on my own despite my neurologist’s statement that statins did not do this and had no further amnesia episodes for the next year. During that time I questioned perhaps a dozen doctors and pharmacists as to any record of Lipitor amnesia, always with a negative response.

Lipitor was again strongly recommended by my NASA doctors on my annual physical the following year, 2000. My doctors had not previously encountered any amnesia side effects from this class of drugs and it was agreed to restart at one-half the previous dose, five milligrams daily.

Six weeks went by and I experienced my second episode of transient

global amnesia. During its 12-hour span, I regressed in memory back to my teens, precisely recalling details of my high school years, but with no awareness of my intervening life.

The same doctors who had treated me the year before made the same diagnosis this time: transient global amnesia, cause unknown. Again they refused to accept any possibility of a Lipitor association, although by now I was convinced that Lipitor had caused my problem. But I remained the only one convinced or even suspicious of a relationship. The prevailing opinion in the medical community was that statins do not do that²⁶.

Alone, I remained on a very isolated pinnacle where I became both the soapbox speaker and audience, defending my conclusion. Even my wife was ready to accept that any relationship of my amnesia episodes with Lipitor was probably coincidental, hinting that the aging process alone does terrible things to the human body. One can hardly argue with that statement but I obstinately saw it differently. These were dark days when despite my conviction, an occasional specter of doubt would reach out momentarily, almost subliminally, suggesting the unthinkable: the possibility of underlying brain disease. Statins don't do this was the stock answer of my doctors.

In desperation I had contacted Joe Graedon of the Peoples Pharmacy^{27a} syndicated column seeking answers to my plea for information. He told me of a new statin study in San Diego and gave me their email contact. Upon receiving my email Dr. Beatrice Golomb of the San Diego College of Medicine statin study²⁸ responded with a telephone call and her very first words lifted a tremendous weight from my shoulders. "I have two more amnesia cases just like yours," she said, "and both are associated with Lipitor use." I was ecstatic and was off and running with my research interest. Dr. Golomb had saved my life, so to speak, and we became close collaborators in the statin side effect study. Joe Graedon meanwhile asked me if I minded if he published my original letter to him in his Peoples Pharmacy column. I saw no problem with that. Soon my website was flooded with emails and abruptly through Peoples Pharmacy stimulation, my website became a focal point for statin damage reports. Within a few months thousands of damage reports came flooding in and, more to the point, our transient global amnesia reports jumped from 3 to 30.

None of these people had any idea their problems could possibly be related to statin use. I made certain that all of my emails were forwarded to Dr. Golomb for the benefit of her studies.

Soon, Dr. Golomb recruited me and Joe Graedon as co-authors in a manuscript she was preparing on “30 cases of statin associated amnesia”. Subsequently, we were appalled to learn that it was refused by one of our major medical journals, the *Annals of Internal Medicine*. I was even more appalled two months later when our manuscript was refused by the *Archives of Internal Medicine*, as well. I am not talking of shoddy, undocumented work here, for both Dr. Golomb and I were thoroughly experienced in the writing of scientific papers. Our paper was so new and counter-current to existing medical philosophy as to be indigestible to the editors and the peer review process. Dr. Golomb gave up at that point and I did not blame her.

In 2003 Wagstaff et al of Duke University submitted a paper to *Pharmacotherapy* titled “The first 60 cases of statin associated transient global amnesia”²⁹ upon their review of FDA’s Medwatch records. From that time to the present (2014) this condition has reached seemingly epidemic proportions in emergency rooms throughout our country with over 9,000 cases of TGA or severe memory impairment being reported to FDA.

Emergency room doctors have hauled out their sometimes dusty medical books and looked with wonder from book to patient as they realize they are seeing what, for many, is their first case of transient global amnesia. These confused patients, asking over and over again, “What has happened to me?” or some similar question, are completely unable to remember the doctor’s explanation offered only moments before³⁰.

For every case of this type of temporary amnesia, thousands of cases of lesser forms of memory disturbance such as extreme forgetfulness, disorientation and confusion have also been reported to statin drug researchers³¹. Most of these cases do not make it to the emergency rooms and are, undoubtedly, extensively under reported.

All of these cases are associated with the use of the statin drugs Lipitor, Zocor, Crestor, Lescol, Mevacor and Pravachol although Lipitor and Zocor appear to have a greater predisposition for these adverse reactions of a cognitive nature³². Sometimes symptoms begin within weeks of starting medication. In other cases several years might pass before the onset of

symptoms. Frequently they have been associated with muscle pain and tenderness, the much more common statin drug side effects.

Although the overwhelming majority of our physicians are very aware of the association of muscle pain with statin drug use, few are aware of the possible effects of statin drugs on cognitive functions³³. Patients, even less aware of this relationship, are reluctant to report amnesia, confusion and altered memory coming on months or even years after statin drugs are started, thinking it is just old age, an inevitable touch of senility or possibly early Alzheimer's disease. When such patients are brought to the doctor's office with these complaints, all too frequently the doctor fails to consider the very real possibility that such side effects might be due to their statin drug, the very drug he or she had placed them on for health maintenance purposes, the very drugs purported to do so much good for public health.

What is Transient Global Amnesia?

The onset of transient global amnesia is abrupt, without the slightest warning to the patient that a central nervous system catastrophe is about to strike³⁴. Suddenly the patient no longer has the ability to formulate new memories, a condition known as anterograde amnesia. Any sensory input during this time will be preserved briefly, if at all, only to disappear completely and forever, as though it never happened. Although consistently aware of their own identities, patients are often perplexed as to their surroundings and the identity of those around them. Characteristically, these patients repetitively question those present about where they are and what is happening but are unable to remember any explanation. To the consternation and ultimate frustration of doctors, nurses and well-meaning companions, they ask the same question, over and over again, sometimes for hours.

In most of these cases disorientation is profound. Many, but not all, of these patients will have an extensive retrograde component to their amnesia extending back many years in their lives. Gone are memories of friends and relatives, marriages and deaths, positions held and occupations learned.

Characteristically, the neurological examination is completely normal except for the amnesia and, after periods of usually less than twelve hours, recovery spontaneously occurs. This restoration of memory takes place

quite rapidly, usually within fifteen to thirty minutes after improvement begins until recovery is complete. During this time patients rapidly become aware of their emergence from amnesia and, to the profound relief of those around them, their repetitive questioning finally ceases.

The syndrome of transient global amnesia, which usually occurs in otherwise healthy middle-aged or elderly people, was first presented to the medical literature by M. B. Bender in the *Journal of the Hillside Hospital* in 1956^{25b}. Since that time it has become a well-described condition, although its etiology has remained an enigma until very recently.

Transient global amnesia may well be a vastly under-reported condition because of the lack of an observer. A patient recovering from such an attack has no recall for the event. For brief episodes of transient global amnesia without an observer, there might be no clue. Dozens, even hundreds, of such brief attacks, measured in durations of less than an hour, may occur undetected in some cases and lead to gross under-reporting.

Anecdotal reporting from observers indicates that routine tasks such as walking or jogging, riding a bicycle or even driving a car appear to be done as usual. One wonders what might transpire in the event there was an associated retrograde element to the amnesia, which included the time period for training for a specific non-routine task such as flying an airplane.

Precipitating factors, events occurring in the 24 hours prior to the attack that might have contributed to it, are many and varied. Moderate to severe physical exertion often precedes an episode; activities such as dragging a deer carcass out of the woods, heavy digging, felling a tree, and laying concrete. Unusual emotional stresses such as newly reported cancer, a death in the family, news of a severe accident, a lawsuit, and violent family arguments can trigger these reactions. Swimming in cold water is occasionally a factor, and some individuals appear to recognize sexual intercourse as a frequent and even consistent trigger. Occasionally, transient global amnesia is seen after routine medical procedures such as venipuncture, minor surgery or application of the Valsalva maneuver, a “grunting” expiration test commonly used to determine cardiovascular responsiveness. Another medical procedure identified as a trigger agent for a growing number of transient global amnesia cases is cerebral angiography. Whether this is due to the patient’s sensitivity to the contrast

agent used, or whether the perfusing fluid transiently alters brain cell metabolism has not been determined.

The advent of the statin drugs has now provided a new contributory factor, one clearly rooted in the biosynthesis of cholesterol and clearly fundamental to neurophysiologic mechanisms³⁵. Reported cases of transient global amnesia associated with the stronger statins such as Lipitor do not reflect its true prevalence because so many cases go undiagnosed and misdiagnosed. Millions of patients now taking this class of drugs--particularly Lipitor, which in 2003 is expected to become the first \$10 billion drug in history⁴--are at significant side-effect risk, and transient global amnesia is just the tip of the iceberg.

For every reported case of transient global amnesia there are hundreds of case reports of impaired memory, disorientation and confusion among an older group of patients that rarely, if ever, get mentioned. All too frequently, this group is willing to accept old age, "senior moments" or incipient senility as the cause, particularly when their physicians are also ignorant about this side effect of the statin drugs.

As to duration and frequency, most patients will have just one attack in their lifetime. The shortest attack of transient global amnesia in their group lasted 15 minutes and the longest 12 hours. All of their cases had reliable observers. Quite understandably, in the absence of an observer, short duration attacks are easily missed. Students of this condition readily appreciate this under-reporting bias by the victim during an attack of transient global amnesia is an almost universal behavior.

Lipitor and Zocor³⁶ seem to have more association with significant cognitive disturbances than their sister drugs Mevacor, Pravachol, Crestor and Zocor. It would seem that very subtle differences exist in this group of HMG-CoA reductase inhibitors and they contribute to variations in the incidences of certain physiological side effects. All side effects seem to be shared among the statins but to different degrees.

Recent studies have shown a strong correlation of TGA episodes with deficiency of valves within the internal jugular vein complex especially while performing the so-called Valsalva respiratory maneuver of G-protection³⁷.

The mechanism of action of statin drugs, that of HMG-CoA reductase

inhibition with its subsequent reduction of cholesterol biosynthesis at the cellular level, brings us tantalizingly close to the ‘final common pathway’ of transient global amnesia, if, indeed, a single pathway exists. The recent identification of cholesterol’s vital role in brain activity as described by Pfrieger³⁸ makes this all the more likely and opens up a fertile area for future study.

On the subject of cognitive impact of statins Medwatch data has reported 2,708 TGAs, 1,971 cases of severe memory loss, 706 cases of cognitive loss and 3,260 cases of extreme confusion from 2004 through 2012 associated with all use of all statins. Additionally for the single statin, Lipitor in the time period 1997 through 2006, 1,965 cases of TGA were reported in a separate study of Medwatch data. This figure is grossly under-reported with no attempt to estimate the brief episodes of TGAs acknowledged by Hodges and Warlow that might increase incidence estimates by ten or one hundred times. This by itself is a formidable figure for incidence of cognitive effect but it is only the very tip of the iceberg. To this must be added the lengthy list of minor effects such as confusion, disorientation, forgetfulness and dementia-like changes closely resembling Alzheimers, diagnosed only after the statin is stopped and improvement occurs.

The Broad Range of Statin Adverse Reactions

Two events occurred in 2001 that were to have an immense effect upon the course of my life. Thanks to the support of Joe and Teresa Graedon³⁹ and the Peoples Pharmacy^{27b} promotion of my statin story, thousands of emails from statin damaged people were pouring into my website. Additionally, the co-author, Dr. Paul Rosch⁴⁰ entered my life by directing me to two very important books on the subject of cholesterol and inviting me to join THINCS, The International Network of Cholesterol skeptics⁴¹. Those books were like seeds germinating in the fertile fields of new concepts that Dr. Rosch’s referral to THINCS had placed me. Kilmer McCully’s “The Homocysteine Revolution”⁴² and Uffe Ravnskov’s “The Cholesterol Myths”^{17b} had a tremendous impact on my thinking. Paul Rosch brought it all together as the enabler who wanted my material brought before the

eminent scientists of THINCS.

FDA opened the shelves of Medwatch in 2006 to those of us wishing to review for ourselves the status of statin adverse drug reports (ADRs). This has been all the more imperative since FDA has been extremely reluctant to report side effect data on the statin class of drugs. I was able to access Medwatch data in 2006. The process was not easy for it meant one must tackle the immense challenge of reviewing manually some 64,000 Lipitor ADRs using the “find” mechanism on one’s PC. This was necessary, I was told, since the appropriate software for reading Medwatch data was available only to FDA and drug company officials. The rest of us had to be content with the time-honored and accurate but painfully slow process of counting each case one by one using the search mechanism on our PC.

What prompted me to do this personal search of what most would agree is FDA’s business were the thousands of emails from statin damaged people telling me of the almost total lack of awareness of most doctors of statin-associated cognitive dysfunction, emotional and behavioral disorders and cases of disabling neuromuscular degeneration. Clearly our doctors have not been informed about most of these reactions, yet I knew from the 30,000 emails I had received through my website (www.spacedoc.com) by 2006 that many thousands of Medwatch reports have been submitted to FDA. In many cases I have been instrumental in helping distraught victims make their FDA report. What is wrong with our ADR reporting system, I wondered? Although all statins were involved I used the Lipitor data for this report. It is important to remember that all statins are reductase inhibitors blocking a single reductase step in the synthesis of cholesterol, so what is true for one is generally true for all statins. The only real variable is strength.

Because of my personal cognitive experience with this drug⁴³, transient global amnesia (TGA) was the first search term I entered. Not unexpectedly, there were 1,302 case reports for TGA in the Medwatch files. Adding the search term “memory impairment” yielded me another 663 cases. This total of 1,965 reports of serious cognitive dysfunction associated with the use of Lipitor seemed to fit quite well with the total numbers of such reports I now have recorded in my repository. I have generally recommended that victims do online Medwatch reporting and had helped

more than a few to do just that.

Gross under-reporting of TGA deserves to be mentioned again here. That is the nature of self-reporting systems. Additionally, only the more severe forms of cognitive dysfunction get reported - the transient global amnesia and severe memory loss. More minor forms of cognitive loss such as confusion, disorientation or unusual forgetfulness are never included, so we should not expect to find them in the database. And I must stress the category of short-term cognitive loss with durations measured in seconds and minutes. By their very nature these will rarely be recognized even by the victim, and yet they might be so critical to a pilot, the crew and passengers. As mentioned earlier their incidence may well be ten or one hundred times greater than full blown TGA attacks. We will never know for certain. The passage of time is too short for recognition, yet special studies have revealed just how common these brief lapses can be⁴⁴.

Applying additional cognitive search terms gave me 222 reports of “dementia,” 523 case reports of “disorientation” and 602 reports of “confusional state.”

I next searched among words that might reflect the curious effects of statin drugs on emotion and behavior now being reported. I found 347 reports using the search terms “aggressiveness,” “paranoia” and “irritability” commonly reported in statin users. Use of the search term “depression” yielded 1,142 reports, of which 118 expressed “suicidal ideation.”

The next search term I entered was rhabdomyolysis, an especially serious form of muscle damage with a fatality rate of 10%⁴⁵. You may recall that it was rhabdomyolysis that led to the Baycol withdrawal from the market. Some 60 deaths in the year 2004 made it untenable for Bayer to continue selling Baycol. Death in these cases is due to the blockage of renal tubules by the muscle cell fragments from ruptured muscle cell membranes and been carried to the kidney by the circulation.

I counted 2,731 Medwatch reports of rhabdomyolysis presumably resulting in 273 kidney failure deaths up to 2006. Applying additional search terms bearing on the muscular system, I found 1325 reports of “myalgia” and 494 reports of “musculoskeletal stiffness”. It should be mentioned here that just recently I have received upgraded Medwatch data

on rhabdomyolysis deaths. A recent study involving Dr. Golomb on the total muscle impact of all statin drugs reported from 2006 to 6 months beyond 2012⁴⁶ found 8,111 rhabdomyolysis hospitalizations for a presumed death toll (from kidney failure) of 811. Somehow the media did not pick up on this. We all recall the media uproar in 2004 resulting in Bayer's removal of Baycol from marketing. I must assume that their being labelled kidney failure deaths prevented the media uprising that almost certainly would have resulted from 811 rhabdomyolysis deaths, had they known.

My response to use of the search term "neuropathy" in 2006 was 1,294 reports to Medwatch. It should be mentioned that almost all of these peripheral neuropathy reports have proven to be very resistant to traditional treatment and now deserve to be called permanent. Using the term "Guillain-Barre syndrome" gave 98 reports, and prompted by hundreds of case reports I have received complaining of leg and arm pain, the search term "pain in extremity" gave 3,498 reports. This figure better reflects the statin neuropathy load.

Next I put in the search term, "hepatitis." Before I tell you the number, I first must qualify it by warning you that there are many different kinds of hepatitis. There is hepatitis A, B, C, cholestatic, autoimmune, fulminating, acute, chronic and viral, including cytomegalovirus. All of these terms are used in this compilation of Lipitor damage reports. However, the overwhelming majority of these reports said simply, "hepatitis" with no qualifier. Since hepatitis always has been a concern from statin use, you must make up your own mind in interpreting the 2,102 total cases that resulted. When I realized that "liver function abnormalities" also was being used in the Medwatch diagnosis list, I used it as a search term, reporting 842 liver function abnormalities in addition to my 2,102 hepatitis cases for a grand total of 2,944.

Since Ralph Edwards⁴⁷ of the World Health Organization reported excessive numbers of peripheral neuropathy and atypical ALS cases associated with the use of Lipitor world wide using their Vigibase data, my next investigation of Lipitor Medwatch data was for search terms that might give a measure of ALS occurrence. "Unusual weakness" turned up 2,516 case reports, "balance disorders" gave 596 responses and "coordination abnormalities" gave 195 responses. Since I have this condition, I can speak

with authority on the subject of balance disorders. A kindly neighbor lady was so concerned on seeing me walk by her home she offered to drive me the rest of the way. Until that moment I was unaware of the effect of my walking on the public eye. Clearly this good Samaritan sensed me as disabled. My transition to walker took place the following day.

The Peoples Pharmacy website carries an unexpected gold mine of ALS incidence data in the following link: <http://www.peoplespharmacy.com/2009/07/31/statins-and-als/> ⁴⁸ Please check out this resource. Joe Graedon started this link in 2007. In it he has invited anyone struck down by statins with symptoms suggestive of ALS (Lou Gehrig's Disease) to comment on their status for the benefit of others. The last time I dug for gold here I was quite certain I had found at least 300 solid cases of ALS with hundreds of others who still might go in that direction since, as many of you understand, it sometimes takes years for ALS to unmask itself. There is no single definitive test. Seven years later (2014) this link remains very active with many hundreds of reports of ALS-like and neuromuscular degeneration cases associated with statin use.

Relevant to diabetes, it is now generally accepted that the incidence rate of new diabetes in statin users is close to 12% - an amazing user penalty for a medicine that is supposed to diminish the risk of cardiovascular disease! I used the search term "pancreatitis" to see how much of this diabetes might reflect organ damage. I found 604 reports of pancreatitis.

I next tried the search term "cardiac failure" and turned up 720 reports. CoQ10 inhibition is felt to be the major contributor to this condition. My next search was "myocardial infarction" out of curiosity as to how many might there be in a group already on Lipitor. The figure was 2,520 - another attention getter - especially when I got 610 additional reports using the search term "coronary artery occlusion." With a total of 3,030 cardiac events in a group already on statins, I wonder just how much protection is being offered. Use of the search term "cerebrovascular accident" (stroke) yielded 1,562 reports, with another 159 inferred by the use of the search term "aphasia."

FDA has a first rate monitoring system but it is grossly deficient for reporting findings back to the medical community. The average primary care physician in our country today, knowing that only a minority of patient

problems get reported to FDA, would be startled to see these figures, especially the ones for cognitive dysfunction, neuropathy, rhabdomyolysis, depression and hepatitis. These are the people who write prescriptions for statin use.

From my 23 years of experience as a primary care doctor, I would say that any doctor attempting to practice medicine without full information on adverse reactions is liable for malpractice. Only with this information can proper, informed judgments for treatment plans be made. It pains me to see my colleagues being maneuvered into this position.

Mechanisms of Action of the Statin Drugs

Ubiquinone and dolichol inhibition is well known to the pharmaceutical industry, which has toyed with the idea of recommending that supplemental coenzyme Q10 be used by patients on statins. Although in 1990 the drug company Merck obtained a patent for the combination of CoQ10 with statins in one prescribed dose⁴⁹, no further action was ever taken on this matter nor did Merck share with the medical community their concerns on the matter. Of interest are the words of their patent justification: to help prevent the inflammation to come.”

This oversight by Merck laid the groundwork for Dr. Sidney Wolfe’s Public Citizen petition of 20 August 2001⁵⁰ and Dr. Julian Whitaker’s 23 May 2002 petition with the Food and Drug Administration (FDA)⁵¹. Dr. Wolfe’s petition called for special “black box” warnings to doctors and patients about the life threatening muscle damage of statin drugs, calling attention to the fact that 81 people had died from statin-related rhabdomyolysis since the time the drugs were first marketed in 1987. Dr. Whitaker’s petition called on the commissioner of the FDA to change the package insert on all statin drugs and to issue a “black box” warning to consumers of the need to take Coenzyme Q10 (CoQ10)^{21b,22b} whenever they take a statin drug however no action was taken on this petition. Of relevance here is the fact that in Canada the Lipitor warning label is strengthened to include warnings not only about CoQ10 depletion but also includes warnings on the closely related L-carnitine deficiencies.

For those statin victims desiring background information on their statin

associated myopathy, neuropathy, ALS-like condition and even cognitive dysfunction, this section should suffice, for this condition can occur in any tissue: muscle, nerve, or brain.

The diminished bioavailability of intracellular CoQ10 and dolichols associated with the use of statins has the potential for seriously increasing oxidative damage and mitochondrial DNA mutations^{52a}. The anti-inflammatory benefits of statins are mediated by their special effect on the NF-kB cellular transcriptases and aggravated by inhibition of such antioxidants as Co-enzyme Q10⁵³. The logical consequence of this is premature aging and the progressive development of such chronic conditions of aging as muscle weakness, burning pain and in-coordination and faulty memory - exactly the clinical picture we are seeing in tens of thousands of statin users.

The clinical responses we are seeing from this process of progressive mitochondrial damage is highly variable, more of a spectrum than any predictable, precise display of symptoms. We first have to accept that most statin users appear to do quite well on statins. This tells me that in some people our mevalonate pathway must take several different forms, by-pass channels if you will, that allow sufficient CoQ10, dolichols, selenoproteins etc to be available despite blockade of the basic mevalonate pathway.

We also find that some persons are completely unresponsive to statins, strongly supporting this possible presence of alternative pathways. In my 23 years of clinical medicine I soon discovered that doctors are fortunate if six out of every ten patients gave the expected response to a given medicine. We soon learn that "That's the way we are made!" There are many ways we biologic organisms evolve to get from A to B.

We also can say that premature aging and the earliest forms of neuropathy and myopathy may not yet be clinically apparent. Dull aches, slight numbness, senior moments and personality change all can be so minor as to escape recognition as possibly significant, so at least some of those who appear to be tolerant may actually have sub-clinical decrement. Just as we have to accept the fact that many, even most patients appear tolerant to statins, many thousands of people have been disabled by statins and for them, their prescribing doctor directly contributed to their problem and, in their eyes, no longer wears a completely white jacket^{52b}.

I have generally categorized the symptoms as cognitive, emotional, neuropathic, myopathic and neurodegenerative but in reality there is much overlap. Hovering above all of these categories is the frequent presentation of tiredness and easy fatigability, pointing directly at deficient energy. Fatigue is the end result of ATP lack, so with sufficient mitochondrial DNA damage fatigue becomes inevitable^{52c}.

The cognitive manifestations of statins may be just episodes of transient global amnesia, or increasing confusion, disorientation and forgetfulness or progressive dementia, which could be called Alzheimers-like, differing only in underlying pathology. Only when one stops the statins and sees regression of symptoms can the true cause be inferred.

So an individual can present with any one or all of these symptoms. It all depends upon what kind of body tissue is the most involved with mitochondrial deterioration. Every cell comes equipped with mitochondria, the energy producers of the cell^{52d}.

Ubiquinone is also vital to the formation of elastin and collagen formation. Tendon and ligament inflammation and rupture have frequently been reported by statin drug users and it is likely that the mechanism of this predisposition to damage is related to some yet unknown compromise of ubiquinone's role in connective tissue formation.

The cells of slowly metabolizing tissue may be composed of only a few mitochondria because its energy needs are minimal. Muscle, heart and brain cells come equipped with hundreds and thousands of mitochondria because of the urgency of their metabolic demand.

There is no way to predict how any one person will respond to this progressive mitochondrial deterioration triggered by statins. Therefore, a cognitively impaired victim may also present with emotional symptoms, painful neuropathy, disabling myopathy or an ALS-like manifestation or with just cognitive dysfunction alone. It all depends on the roll of the dice^{10b}. Since the year 2000 I have devoted my full time to a study of the adverse reactions of statin drugs and the mechanisms by which they influence human physiology. My website at www.spacedoc.com with its busy forum is based upon my receipt of some 30,000 emails from statin damaged people and contains some 250 articles on the subject of statin side effects. In the year 2000 statin associated transient global amnesia was

unknown. Four years would pass before excess rhabdomyolysis deaths would take Baycol off the market. Despite the apparent benefits claimed in many of the clinical trials, men like Drs. Uffe Ravnskov and Kilmer McCully strongly doubted cholesterol causation and by 2002 Dr. Ora Shovman already had written his review of the “Anti-inflammatory and Immuno-modulatory Properties of Statins, exposing the truth about reductase inhibitors. Yes they lowered cholesterol but it was their anti-inflammatory effects mediated by nuclear factor kappa B (NF- κ B) that lowered coronary risk. Cholesterol lowering by mevalonate blockade had nothing to do with it. After four decades of hype by Big Pharma and the drug companies acceptance was to come slowly. Even now doubters remain but the evidence can no longer be denied. Statin doses of the future must be those that enhance the NF- κ B mechanism without adversely influencing our vital mevalonate pathway..

Conclusion and Key Issues

I have every reason to believe that statins will continue to sell but expect some falloff in sales figures as the medical community increasingly accepts inflammation rather than cholesterol causality and begins to accept much lower statin dosing levels. Since cholesterol no longer is the accepted cause of atherosclerosis and it is now back to whole milk, eggs and real butter, it makes no sense to continue to dose statins at 20, 40 and 60 mg levels to lower cholesterol. Cholesterol is not the problem. All we are doing at those dosage levels is creating more adverse reactions from mevalonate pathway blockade.

Dosing statins at cholesterol lowering doses does nothing but increase adverse reactions by the inevitable blockade of the mevalonate pathway decreasing the synthesis not only of cholesterol but also of CoQ10, dolichols selenoproteins and other biochemicals vital to cellular function.

We have learned that statins have two primary actions. They were designed to inhibit the reductase step in the mevalonate pathway thereby reducing the synthesis of cholesterol but more recently we have learned that there is a different side of statins one that affects the intracellular transcriptase nuclear factor kappa B mechanism leading to suppression of inflammation and immune functions. This is the mechanism that reduces

coronary risk but also leads to increased susceptibility to cancer.

Lack of sufficient CoQ10 leads to diminished energy production and increased tendency for congestive heart failure. Diminished dolichols lead directly to diabetes. We who study these reactions knew that diabetes was inevitable years before the first cases appeared. The greater the statin dose the greater these side effects.

The only meaningful screening test for coronary artery disease is (hs)CRP, a test for inflammation that correlate well for predisposition to heart disease. The JUPITER study proved the validity of this test as well as the irrelevance of cholesterol in screening for coronary proneness.

If your present statin dose lowers cholesterol you are giving too much statin.

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Chapter Seventeen

Systemic Evaluation of Statin Therapy Side Effects. Do the Accrued Adverse Effects Outweigh the Benefits?

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Abstract

Statin studies have shown that the rate of adverse side effects that surface in post-marketing studies is very much greater compared to those reported in company sponsored clinical trials designed to obtain approval. This may be due to the highly selective nature of such trials that are conducted in populations not representative of those who ultimately receive statins. As a consequence, the overall adverse effects on the population have not been adequately determined.

A comprehensive objective review of articles pertaining to statin therapy was conducted to clarify their role within contemporary clinical practices. These showed that statin therapy leads to both beneficial and detrimental effects. Statin side effects included an increased risk of diabetes, myopathy, cognitive deficiencies, amnesia, peripheral neuritis, premature cataract development, erectile dysfunction, chronic fatigue syndrome, intra-cerebral bleeding, interstitial pneumonitis, and rhabdomyolysis. Some recent studies have also documented that statin therapy increases the risks of atherosclerosis, Parkinson's disease, cancer and congestive heart failure (CHF). These results are clearly alarming and provoke the possibility of not only the lack of primary cardiovascular protection by statin therapy but highlight the very real possibility of augmented cardiovascular risk in women, patients with diabetes, octogenarians as well as the young.

Introduction

The endovascular revolution has brought about unprecedented changes in

our cardiovascular practice over the last twenty-five years. In the course of this insurgence, we contemplated that gene and stem cell therapy would supplant all technologies. However, after phase three human trials and more than 7 billion euro squandered globally on research and development, all that we have attained is the realization that we are remote from any ground breaking clinical outcome.

Cholesterol is established in every human cell body, and plays significant roles as part of cell walls or membranes, in the manufacture of hormones, and helps promote the absorption of fat from our diet. Cholesterol and fat is insoluble in the blood and binds with apo-proteins in order to keep them soluble. Low-density lipoproteins (LDL) are the main types involved in transporting cholesterol in the blood. It is the vehicle that mobilises cholesterol, but not a marker as wrongly labelled.

Recently statins have gotten bad press in relation to causing adverse side affects such as muscle pain and inflammation, increased risk of development of diabetes mellitus, and neurological side effects. Studies show that the rate of adverse side effects in post-marketing studies is greater than that found in the pre-marketing studies. This is due to the highly selective nature of clinical trial populations. The populations may therefore not represent those who ultimately receive statin therapy. Consequently, the overall adverse effects are not determined.

Cholesterol is crucial for energy, immunity, fat metabolism, leptin, thyroid hormone activity, liver related synthesis, stress intolerance, adrenal function, sex hormone syntheses and brain function. We must keep in mind before prescribing a statin therapy that the body has increased its cholesterol level as a defensive mechanism. For example seasonal level adjustments and the effects on metabolism must be considered, especially in northern countries that lack sunshine in winter.

Statin Induced Side effects

Diabetes Mellitus

Diabetes is a life-long medical condition, which inhibits the body's natural process of effectively using energy from the intake of food. Those with diabetes tend to have a higher disposition towards cardiovascular related

events. Patients diagnosed with diabetes are often concomitantly prescribed a statin therapy, which is thought to combat the rising levels of cholesterol, thereby reducing cardiovascular risk.

Conversely, a study by the US veterans affair healthcare system conducted on 15 million veterans in 10 hospital centres in the US established that statins affect both fasting and postprandial glucose levels by inducing a state of hyperglycemia in diabetic as well as non diabetic patients.¹ A sub-analysis of the JUPITER study showed that statin therapy can in fact induce full blown type 2 diabetes in women.²

This was shown in the sub-study of PROVE-IT TIMI 22, which assessed intensive lipid lowering in diabetics. Results showed there was a significantly increased risk (6 %) of developing an elevated glycated hemoglobin (HBA1c) level in both diabetics and non diabetics.³ Furthermore, Huptas et al. demonstrated that daily atorvastatin (10 mg/day) statin therapy actually encouraged insulin resistance in patients with a metabolic syndrome.⁴

Culver et al. investigated statin use and its risk of developing diabetes in 153,840 post-menopausal women without Diabetes Mellitus.^{5a} Results documented 10,242 incidences of diabetes over 1,004,466 person-years of follow-up. Statin use at baseline was associated with an increased risk of diabetes and this association remained after adjusting for other potential confounders and was observed for all types of statin medications. The authors concluded that the increased risk for diabetes in post-menopausal women is a medication class effect of statins. These results confirmed that of the JUPITER sub-analysis.

A critical appraisal of the JUPITER trial by de Lorgeril et al. elucidated that the results of statin therapy trials do not support the use of statin treatment for primary prevention of cardiovascular diseases.⁶ Prescribing a statin in old age has a 9 % increase in the risk of developing diabetes.^{7a} It is another iatrogenic risk factor that must be avoided and it is mandatory to add glucose level testing to the list required for monitoring patients on statin therapy, and is equally as important as liver function and creatine kinase (CK) tests.

Preiss et al. conducted a meta-analysis of data from 5 major statin trials. There was an increased incidence of new onset diabetes with statin therapy,

and evidence of a dose dependent association by assessing intensive versus moderate dose therapy.^{8a} As well as a dose dependent association, large scale randomized controlled trials demonstrated differences in risk between individual statin medications. Pravastatin tends to reduce risk of new onset of diabetes, while atorvastatin, rosuvastatin and simvastatin together significantly increase risk of new onset of diabetes.⁹

A meta-analysis of individual data from 27 randomised trials published in the Lancet revealed an excess incidence of diabetes of 0.1 % per year in patients at low risk of developing vascular disease.¹⁰ The Cholesterol Treatment Trialists' (CTT) Collaboration authors reported a 10 % increase in the relative risk of developing diabetes while taking statins, yielding an estimated excess of 5 new diagnoses per 1000 people over 5 years.¹¹ Data from the JUPITER trial by Mora et al, showed a 25 % increase in frequency of physician reported incidence of diabetes, and a 50 % increase in women alone, corresponding to an estimated 11 new diagnoses per 1000 women over 1.9 years.¹²

In 14 primary prevention trials that involved 46,262 participants, treatment with statins was associated with an increase in the absolute risk of diabetes of 0.5 %.^{13a} The study found that only the risk of developing new onset diabetes mellitus was significantly higher in patients taking statins than in those taking a placebo.^{13b}

A meta-analysis of 6 statin trials that included 57,593 participants revealed a 13 % increase in the relative risk of new-onset diabetes.¹⁴ Similarly, a meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes.^{7b}

With increasing incidence of new diagnosis, costs may spiral. A study by Briggs et al. predicted that prescribing statins to everyone over the age of 50 years will lead to 12,300 diagnoses of diabetes.^{15a} The total extra cost of statin treatment from the drug alone is estimated at £180m.^{15b} Prescribing statins to everybody over 30 years old is estimated to produce 24,400 excess diabetes diagnoses at a cost of £360m.^{15c}

Statins may increase the risk of new-onset diabetes, particularly in patients already at risk of developing the disease by disrupting a number of regulatory pathways including insulin signalling, which may affect insulin

sensitivity, pancreatic β -cell function, and adipokine secretion.^{16,8b} A study by Cederberg et al. showed that statin treatment increased the risk of type 2 diabetes and was attributable to decreases in insulin sensitivity and insulin secretion in a study of 8,749 non-diabetic participants.¹⁷

From the literature we can see there is overwhelming evidence to suggest that prescribing statins to non-diabetics can lead to disastrous effects such as full-blown development of type 2 diabetes. Statins manipulate glucose metabolism as a consequence of inhibitory effects on adipocytes. They induce insulin resistance through reduction in insulin-stimulated glucose uptake with a strong impact on glycemic control in non-obese patients. Patient metabolic conditions as well as whether statins can amend or impair insulin resistance, and ultimately type 2 diabetes mellitus impairs the poise of utilizing statins and its clear outcomes.

Myopathy and Incapacitation

Myopathy is a disease of the muscle fibres, which leads to dysfunction and muscle weakness as a result. There is an increasing amount of evidence to suggest that statin therapy induces myopathy as an adverse effect in those prescribed statins. In fact, myopathy is the most common adverse effect of statin treatment, manifested by muscle aches and pains, weakness, instability, and easy fatigue.^{18a,19a} It is seen most often in women and elderly people.^{20a,21,22a,23a} In one randomized trial of 1,016 healthy men and women given statins or a placebo, 40 % of the women taking statins suffered exertional fatigue or decreased energy.^{20b} Other studies demonstrated increased muscle fatigability of 30 %.^{24,25}

Statin therapy induces inflammatory myopathy, including necrotizing autoimmune myopathy with immunosuppression. Statin-related myopathy can last for 12 months. Myalgia or myopathy were the most common category of statin-related events, affecting 27 % of patients who had any statin-related event documented and 4.71 % of all patients.^{26a} Among the 3,858 patients who had a statin-related event, had the original statin discontinued, and were then re-challenged with another statin, a second statin-related event was subsequently documented for 510 (13.2 %) patients. Only 381 (9.9 %) of these patients had myalgia or myopathy that

was severe enough to warrant discontinuation of the re-challenge statin.^{26b} Prescribing statins to everyone over the age of 50 years is predicted to lead to 1,200 excess cases of myopathy, with a total extra cost of statin treatment from the drug alone estimated at £180m.^{15d}

A cross sectional analysis of data from the National Health and Nutrition Examination Survey database by Buetter et al. similarly showed that the occurrence of muscle pain in patients prescribed with a statin therapy was 50 % greater when compared to patients with no prescription.²⁷ A retrospective cohort study that included 13,626 participants taking statins and 32,623 controls found a greater incidence of musculoskeletal disorders overall, and injuries in those taking statins.²⁸ Sinzinger et al.^{22b} has reported that muscular weakness and pain occur in 1 out of 4 statin treated patients who exercise regularly. They also noted that 17 out of 22 professional athletes with familial hypercholesterolemia (FH) treated with statins stopped because of that particular side effect.^{36a,23b} Golomb et al.^{20c} performed a randomized controlled trial that included 1,016 healthy men and women with high LDL-C. Participants were divided into 3 groups that were given 20 mg simvastatin, 40 mg pravastatin or placebo. After 6 months treatment, 40 % of the women on statin treatment experienced adverse effects to energy or exertional fatigue.^{20d}

All statins have been reported to cause myopathy, with the severity ranging from asymptomatic increases in creatine kinase to myalgia and myositis to fatal rhabdomyolysis, commonly characterized by massive muscle necrosis, myoglobinuria and acute renal failure.^{29a,30,31} People on statins may have muscular problems although their CK is normal,³² and even people on statins without any symptoms may have microscopic evidence of muscular damage.³³ Myopathy is dose dependent and may occur after therapy has been tolerated for up to 1 year.^{29b}

It is our experience that patient's who present with statin therapy-induced myopathy, have complete resolution of symptoms relatively quickly, or upon cessation of therapy. Some patients can take between 9 and 12 months to feel near normal again, or may present with more severe side effects such as muscle damage, rhabdomyolysis or in some cases complete incapacitation as a result. Reviewing the literature demonstrates a definitive link between statin therapy and myopathy. This should be tentatively taken

into account when making the decision to prescribe a statin therapy.

Amnesia and Incapacitation

Statin therapy has been directly associated with memory loss.^{20e,34a,35} Most reports were from individuals older than 50 years of age. Time to onset of the impairment was highly variable, ranging from 1 day to years after statin exposure. An association between cognitive impairment and a specific statin, a specific age group, a particular statin dose, or concomitant medication use was not observed. Furthermore, the cognitive impairment did not appear to be associated with fixed or progressive dementia, such as Alzheimer's disease, and was not detectable in controlled clinical trials measuring longer-term cognition.^{36b,37,38}

A large-scale study by Strom et al. including almost a million subjects compared a statin user to a non-statin user group. The authors observed a strong association between first exposure to statins and acute memory loss, which was diagnosed within 30 days immediately following exposure. The increase in memory loss was 4.4 times compared with non-statin users. The non-statin lipid lowering drugs increased memory loss 3.6 times compared with people not on lipid lowering medicines. Both statin and non-statin drugs substantially dented acute memory to a similar degree. They concluded that either all lipid-lowering drugs cause acute memory loss regardless of drug class or the association is the result of detection bias rather than a causal association.³⁹

Memory problems were reported for 0.06 % (n = 70 / 107035) of patients in a study by Zhang et al.^{26c} In a study of 143 patients with memory loss or other cognitive problems associated with statin therapy, they reported that 90 % of them improved, sometimes within days of statin discontinuation.⁴⁰

In a study by Padala et al., older statin-treated patients with Alzheimer's disease were asked to stop their statin treatment. Twelve weeks later, their performance on several cognition tests had improved significantly and after having started the treatment again, their performance on the tests worsened significantly.⁴¹ There is a strong argument for the view that statin treatment may cause adverse central nervous system effects. In a study by Sahebzamani et al. of adverse events from statin treatment reported to the

FDA, there was a disproportionately greater incidence of adverse cognitive events reported by patients who were treated with lipophilic statins.⁴²

Reports of memory loss, or cognitive deficiencies are difficult to cultivate from patients on a statin therapy. This risk factor is difficult to measure since it is not a quantitative measure, but nonetheless, evidence from the literature has shown a strong link between statin therapy and amnesia.

Peripheral Neuritis

Peripheral neuritis occurs as a result of damage to the peripheral nerves. This in turn causes pain, weakness, and numbness. There is a dearth of published studies that examine statin induced peripheral neuritis. Although, statin therapy has been associated with a wide range of adverse events including neuropathy.^{19b,43} Gaist et al. conducted a study on 465,000 people in Denmark. They asked all patients who had polyneuropathy of unknown cause, how many were on statin treatment. This was then compared with the general population in the county. They calculated that the risk for definite polyneuropathy was 16-times higher for current statin users than for non-users, and even higher for those who had used statins for more than 2 years.⁴⁴

Arterial Calcification and Sclerosis

Arterial calcification and sclerosis is a silent disease, which can remain asymptomatic throughout the life of an individual, and may ultimately lead to a life-threatening vascular event. It is associated with accumulation of LDL, macrophages, T cells, smooth muscle cells, proteoglycans, collagen, calcium and necrotic debris in the vessel wall.⁴⁵ Arterial calcification can result from an initial injury to the vascular wall, where the endothelial cells have been disturbed, or a change in velocity of the blood on the intra arterial wall. This leads to endothelial dysfunction and inflammation.

Reducing carbohydrates, as opposed to fat, seems to have more favourable effects on atherogenic dyslipidemia, inflammation, thrombogenic and atherosclerotic surrogate markers, hence the development of atherosclerosis, heart disease, diabetes, obesity and the

metabolic syndromes.^{46,47,48,49,50,51,52,53,54} Couse et al. assessed whether statin therapy could slow progression and/or cause regression of carotid intima-media thickness (CIMT) over 2 years, and found that Rosuvastatin did not induce disease regression.⁵⁵

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial reported no difference in carotid intima-media thickness in patients with heterozygous familial hypercholesterolemia who were treated with simvastatin and ezetimibe or with simvastatin and placebo, despite significantly greater LDL-C lowering with the combination.⁵⁶ In the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study,^{57a} 1,873 subjects with mild to moderate aortic stenosis were randomized to ezetimibe 10 mg/day and simvastatin or to placebo. After 4 years, combination therapy with ezetimibe reduced LDL-C by 61% as compared with the effect of placebo administration. Although there was no effect on requirement for aortic valve surgery.

In 2 randomized double blind trials, the effect of statin therapy on progression of coronary artery calcification (CAC) was studied. Over a period of 12 months, intensive atorvastatin therapy was unable to attenuate CAC progression compared with standard atorvastatin therapy.⁵⁸

Literature shows that statin therapy has reduced the incidences of cardiovascular related events however, no definitive link has been made between statins and reduction in atherosclerosis. This absence of association between cholesterol levels and the degree of atherosclerosis in unselected people was originally described in 1936.⁵⁹ Similarly, over 50 years ago, heart surgeon Michael DeBakey and his team found no correlation between blood cholesterol levels and severity of atherosclerosis in patients undergoing surgical treatment of atherosclerotic cardiovascular disease.⁶⁰ The fact is that older adults with low levels of cholesterol are just as atherosclerotic as those with high levels.⁶¹ Despite the many contradictory findings, the advocates have praised statins as ‘miracle drugs’ which are ‘the best anti-atherosclerotic insurance’.⁶²

Premature Cataract

Cataract is a clouding of the lens in the eye, leading to impaired vision. It is

caused by coagulation of protein within the lens in a small area, which is the clouded area. Statin therapy has been associated with a wide range of adverse events including cataracts.^{5b,19c,34b,63a,64a,65a} For normal healthy individuals who are using statins as a method of primary prevention, it was discovered that for every 10,000 people taking a statin, there were 307 extra patients with cataracts.^{63b,66a,67a} There is in fact a 50 % probability of cataract development in statin users at an earlier age than non-statin users, who develop them at a significantly later age.^{64b} These published findings,^{65b,66b,67b,68,69,70,71,72,73} although not in a large number may represent a further clinical side effect which is theoretically linked to statin therapy.

Cancer

Cancer is the notorious silent killer. As well as the life-threatening genetic link, there is strong evidence that low cholesterol and statin use, in particular, are both associated with an increased risk of cancer. The carcinogenicity of lipid lower drugs has been demonstrated in animal studies.⁷⁴ Hypo-cholesteremic patients have a higher incidence of intracerebral bleeds, depression and cancer.^{75a} One systematic review found evidence that statin therapy increased risk of non-melanoma skin cancers.⁷⁶

Vinogradova et al. documented that long-term statin use was associated with an increased risk of colorectal cancer, bladder cancer and lung cancer.^{67c} The ILLUMINATE trial was undertaken to investigate a drug that increases HDL but the investigators found that the drug actually resulted in an increased risk of mortality and morbidity, with high cancer rates.⁷⁷ A study on statin use and thyroid cancer showed that statin use was indeed associated with thyroid cancer in female patients.⁷⁸

The West of Scotland Coronary Prevention Study (WOSCOPS) trial evaluated 40 mg/day pravastatin in men with hyper-cholesterolemia reported an increase in the overall incidence of cancer.⁷⁹ A study of long-term statin use and the risk of invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) demonstrated that current users of statins for 10 years or longer had a 1.83-fold increased risk of IDC and a 1.97-fold increased risk of ILC, compared to never users of statins. Among women

diagnosed with hyper-cholesterolemia, current users of statins for 10 years or longer had more than double the risk of both IDC and ILC compared to never users.⁸⁰

The CARE trial was a secondary-preventive trial of pravastatin and included 4,159 patients with MI and average cholesterol levels. Half of the patients were administered 40 mg pravastatin, half of them placebo. After 5 years treatment, the most serious adverse event was breast cancer, which occurred in 12 of the women (4.2 %) in the pravastatin group but in only 1 of the women (0.34 %) in the placebo group.⁸¹ Moreover, at least 9 cohort studies have shown that low cholesterol measured 10-30 years previously is a risk factor for cancer later in life.⁸²

The PROSPER trial examined pravastatin in elderly individuals with a history of, or risk factors for, vascular disease. Half of them were given pravastatin, the other half a placebo. At follow-up 3.2 years later, a substantial number of patients had died from cancer. Furthermore, the cancer difference between the two groups increased year over year.^{36c}

In the two first simvastatin trials, 4S and Heart Protection Study (HPS), more patients in the treatment groups were diagnosed with non-melanoma skin cancer.^{83,84a} Another statin trial where cancer occurred more often in the treatment group is SEAS. In this trial, 1,873 patients with various degrees of aortic stenosis and elevated total cholesterol were included. Half of them were treated with simvastatin and ezetimibe, the other half with a placebo. After 4.3 years treatment, cancer appeared in 105 patients (11.1 %) in the treatment group, but only in 70 patients (7.5 %) in the control group.^{57b}

The literature shows that evidence linking statin therapy use to cancer development in general, let alone a specific cancer type is mostly heterogeneous. There has been to date no cell based analysis data that evaluates the specific causative effects of statins within the body that lead to the development of cancers. It is hypothesized that in women, the lowering levels of oestrogen and progesterone have a direct effect on cholesterol levels, especially in women over the ages of 50. The body begins to produce more cholesterol to balance decreasing levels of oestrogen and progesterone due to menopause. Women then receive statins, which in turn may increase the risk of cancer development.

Erectile Dysfunction

Case reports and clinical trial evidence supported the suggestion that statins can cause erectile dysfunction (ED). Some information on possible mechanisms was obtained, but the mechanism remains uncertain.^{85a} A recent study of 150,000 patients who were taking statins showed unacceptable side effects, including erectile dysfunction in 20 % of participants, resulting in discontinuation of the drug.^{26d}

ED in association with statins was first reported by Halkin et al. where both lovastatin and pravastatin separately caused ED in a 57-year-old man.⁸⁶ Jackson reported 5 cases of ED with simvastatin at doses of 10 mg and 20 mg.⁸⁷ Sexual function was restored within 1 week of stopping the drug. Two patients were further re-challenged only to find that impotence recurred.

In the 4S study, a prospective randomized trial, 37 patients of 1,814 on simvastatin developed ED, as did 28 of 1,803 on a placebo.^{84b} The Australian Adverse Drug Reaction Advisory Committee (ADRAC) reported 42 cases of ED in association with simvastatin.⁸⁸ Details of cases of ED on lipid-lowering therapy reported to the UK Committee on Safety of Medicines (Yellow Card Scheme) identified 170 cases of ED.^{85b}

Erectile dysfunction (ED) is not mentioned in most statin trials, however, when specifically examined, around 20 % of men appear to be affected.⁸⁹ It is hypothesized that statin therapy may reduce levels of testosterone thereby exacerbating the symptoms of ED.⁹⁰

Chronic Fatigue Syndrome

Statin therapy has been associated with decreased energy and exertional fatigue.^{20f} Myopathy, which is the most common adverse effect of statin treatment, is manifested by muscle aches and pains, weakness, instability, and easy fatigue.^{18b,19d}

A double blind randomised controlled trial that compared 1,016 low risk patients receiving simvastatin 20 mg or pravastatin 40 mg with placebo showed that both drugs had a significant adverse effect on energy/fatigue exercise score with 40 % of women reporting reduced energy or fatigue

with exertion.^{20g}

Benign Essential Tremor & Parkinson Plus Syndromes

Benign essential tremor also known as essential or familial tremor is a neurological disorder marked by recurrent shaking. Parkinson plus syndromes are a group of neurological disorders, which mimic Parkinson's disease and are difficult to distinguish and diagnose as a result. Cholesterol levels are the main determinant of coenzyme Q10, an important antioxidant and mitochondrial electron receptor.⁹¹ Coenzyme Q10 is neuroprotective and there is evidence that it may slow the progression of Parkinson's disease.⁹² Parkinson's disease and ataxia like syndrome are increasing in nature in a subcategory of old patients. Cholesterol is a critical component of neuronal cell membranes and synapses, and plays an important role in their proper functioning. A strong association between lower cholesterol and Parkinson's disease risk has been reported, such that each mmol/L increase in total cholesterol was accompanied by a 23 % decrease in the risk of developing Parkinson's disease. The risk reduction was significant in women but not in men.⁹³

With this positive effect however, one should consider, is prescribing a patient with a tremor syndrome unethical due to the known adverse side effects that the patient may experience? This should be tentatively considered when prescribing statins in particular patients.

Intra-Cerebral Bleeds

High cholesterol levels have been found to be protective in the elderly against intra-cerebral bleeds and Hypo-cholesteremic patients had higher incidence of intra-cerebral bleeds.^{75b} Therefore, avoiding statins should be considered for patients with a history of intra-cerebral haemorrhage (ICH).⁹⁴

Meier et al. analysed 311 consecutive patients who received intra-arterial thrombolysis. Statin pre-treatment was present in 18 %. The authors demonstrated that prior statin use is associated with a higher frequency of any ICH after intra-arterial thrombolysis.⁹⁵ Long-term treatment with

lovastatin was associated with a significant reduction of fibrinogen levels and platelet aggregation induced by ADP in type-IIa hyper-cholesterolemic patients.⁹⁶

Eichel et al. recruited 399 patients with ICH, of which 101 (25 %) were using statins. Treatment with statins prior to ICH failed to show a significant impact on outcome in this analysis despite lower haematoma volumes.⁹⁷

The literature predominantly shows that statin therapy is in fact associated with a higher risk of intra-cerebral haemorrhage. Simvastatin treatment depresses blood clotting, which leads to reduced rates of prothrombin activation, factor Va generation, fibrinogen cleavage, factor XIII activation, and an increased rate of factor Va inactivation.⁹⁸

Interstitial Pneumonitis

Statin-induced ILD (interstitial lung disease) has been reported with most statins, suggesting that statin-induced ILD is a class effect and not a specific statin effect.⁹⁹ Kim et al. outlined a case study of statin-induced interstitial pneumonitis caused by rosuvastatin.¹⁰⁰ Another case study by Lantuejoul et al. described an incident of statin-induced fibrotic nonspecific interstitial pneumonia. The authors proposed that because statins are increasingly prescribed, statin-induced interstitial lung disorders might be more frequently observed.¹⁰¹

A large-scale cohort study of over 1.4 million patients from the Quebec health administrative databases was carried out between 1990-2005. 6,665 possible or probable cases of ILD were identified during follow-up.¹⁰²

Congestive Heart Failure

Congestive Heart Failure (CHF) is characterized by a build up of fluid in the body, which emanates from a progressive decrease in pumping power of the heart. Briggs et al. examined 136,936 patients for side effects of statins. Of those prescribed higher potency statins, 16.3 % were diagnosed with CHF. Of those prescribed lower potency statins, 17.5 % were diagnosed with CHF. In total, there were 3,629 cases of new onset diabetes in the first

2 years of follow-up study population. New cases demonstrated a slightly greater prevalence of congestive heart failure.¹⁰³

Overall, statins have been linked with CHF but studies are mixed in their conclusions.

Rhabdomyolysis

Rhabdomyolysis is the breakdown of muscle tissue resulting in the release of muscle fibre contents i.e. myoglobin into the blood. This protein and its determinants are harmful to the kidneys, which are responsible for filtering it out of the blood. Preiss et al. predicted in an analysis of data from 5 major statin trials, an 11.3 % enhanced risk of rhabdomyolysis with utilization of high-dose statin therapy,^{8c} while prescribing statins to everyone over the age of 50 years is predicted to lead to 200 excess cases of rhabdomyolysis.

In a systematic review of statins with about 35,000 people and 158,000 person years in both treated and placebo groups, rhabdomyolysis was diagnosed in 8 treated and 5 placebo patients, none with serious illness or death.¹⁰⁴ Taylor et al. found that 0.03 % of patients experienced rhabdomyolysis, in a total of 17.3 % participants that experienced an adverse event.¹⁰⁵

Rhabdomyolysis represents the least frequent side effect of statins. Although it is a potentially fatal complication caused by skeletal muscle breakdown, which is released into the blood. The rates of rhabdomyolysis have been estimated from clinical trial and cohort data as 3 per 100,000 person-years during statin treatment.¹⁰⁶

Young Children and Adolescents

When taking the previously discussed factors into account, there is a need for definitive long-term arduous data to support the use of statins, which begin in childhood. We can see that there has been a plethora of studies investigating the effects of statins in adults, however this has not been shown to any extent in children. Therefore estimating the risks in relation to statin use for children and young adults is difficult. But one can see that the risks would probably not be zero in comparison. From the literature discussed, statins do lead to increased risk of development of a number of

serious side effects such as diabetes, peripheral neuritis, ICH, interstitial pneumonitis, and rhabdomyolysis.

Young adults often suffer from a genetic form of high cholesterol known as Familial hypercholesterolemia (FH). The principal treatment for FH in young adults is lifestyle modification. The recommended dietary approach for lowering LDL-C is a low saturated fat diet, devoid of trans-fat and high in fruits and vegetables, with an emphasis on fibre. Dietary advice trials have shown both the safety and the benefits of this approach in the general paediatric population,^{107,108,109} and a meta-analysis of nutrition and physical activity trials shows that lifestyle modification can lower LDL-C and improve other cardiovascular disease risk factors in obese children.¹¹⁰

Various supplements have been used to lower LDL-C and total cholesterol.^{111,112} Stanol esters have been evaluated in several studies of children with hyper-cholesterolemia, and regular intake in the form of prepared muffins, margarine spreads, or chews shows reasonable but small decreases in LDL-C of 5 % to 7 %.¹¹³ Red rice yeast extract has to date the strongest LDL-C reducing effect described in the adult literature. One paediatric trial tested a combination of red yeast rice extract and policosanols, and produced an 18 % lowering of LDL-C in hyper-cholesterolemic children over the course of 8 weeks.¹¹⁴

Fibre is recommended as a supplement that produces a satisfactory improvement in LDL-C, depending on the baseline diet.^{115,116} Bile acid binding resins have been shown in several paediatric trials to lower LDL-C by as much as 15 %.^{117,118} Their use has been hampered by difficulties with adherence due to unpalatability and adverse effects such as bloating and constipation.¹¹⁹ Fibrates have been used extensively in children and adolescents and again show similar efficacy to adults, with better tolerability than bile acid sequestrants but lesser efficacy in reducing LDL-C levels.^{120,121} Niacin has previously been used extensively in adolescents and has similar lipid-lowering efficacy to bile acid sequestrants and fibrates.¹²² Ezetimibe has been shown to reduce LDL-C levels by 20 % in children with homozygous FH.¹²³

In adolescents, statins should not be used as a principal method of lowering cholesterol; rather lifestyle changes and supplements should be utilized where possible. Where adolescents are concerned, compliance to

lifestyle changes such as diet change is often an issue. But examining the possible side effects that can occur with prolonged use, statins in adolescents may need to be avoided at all costs, or at least only as a final resort.

Conclusion

From the literature discussed, there is an increased risk of diabetes, myopathy, cognitive deficiencies, peripheral neuritis, cataract development, erectile dysfunction, fatigue, intra-cerebral bleeding, interstitial pneumonitis, and rhabdomyolysis. Evidence shows that statin therapy failed in primary prevention but helps patients through secondary prevention with reduction of non-cardiovascular death over 10 years. The unexpected increase of cancer and congestive cardiac failure in statin users must be scrutinised.

The majority of company funded drugs trials in the past have overestimated the benefits of statin therapy, while grossly underestimating their harms. Results provoke the possibility of not only the lack of primary cardiovascular protection by statin therapy but highlight the very real possibility of augmented cardiovascular risk in women, octogenarians, patients with diabetes and the young.

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Chapter Three

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- 2a. Centers for Disease Control and Prevention. Table 26. Leading causes of death and numbers of deaths, by sex, race, and Hispanic origin: United States, 1980 and 2007,. In: National Center for Health Statistics, editor.; 2010.
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Chapter Eight

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* For the sake of simplicity, IHD and CHD are used as they were in the original cited papers but are used interchangeably in this chapter.

Chapter Nine

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Chapter Ten

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** The importance in the degree of stretching of an artery, as a mechanical factor for atherosclerosis, is known since the early fifties.^{68a}

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Chapter Twelve

* I have only used references where I have stated something that is highly controversial, little known, or difficult to find easily e.g. data on haemophilia. Everything else can be rapidly be confirmed by using Google or Pubmed <http://www.ncbi.nlm.nih.gov/pubmed>

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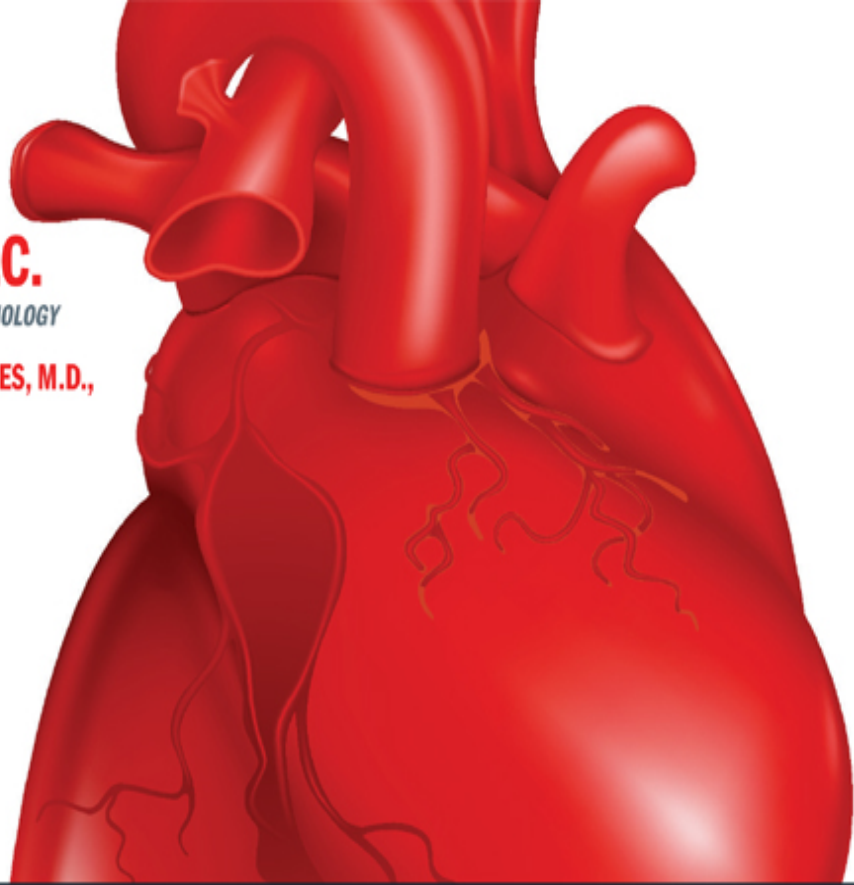
JONNY BOWDEN, PH.D., C.N.S.

BEST-SELLING AUTHOR OF *THE 150 HEALTHIEST FOODS ON EARTH*

STEPHEN SINATRA, M.D., F.A.C.C.

BEST-SELLING AUTHOR OF *THE SINATRA SOLUTION: METABOLIC CARDIOLOGY*

FOREWORD BY **MICHAEL R. EADES, M.D.**, AND **MARY DAN EADES, M.D.**,
CO-AUTHORS OF THE BESTSELLER *PROTEIN POWER*



THE

GREAT CHOLESTEROL

MYTH



WHY LOWERING YOUR CHOLESTEROL
WON'T PREVENT HEART DISEASE—
AND THE STATIN-FREE PLAN THAT WILL



“The Great Cholesterol Myth goes far beyond the standard information and advice for anyone worried about heart disease. The style is breezy and easy to read, but the information is solid and will surprise many readers. A must for anyone who needs to combat heart problems.”

—JOE GRAEDON, M.S., AND TERESA GRAEDON, PH.D., *New York Times* best-selling authors of *The People’s Pharmacy*

“The simplistic view that dietary and serum cholesterol are the primary causes of heart disease and heart attack is no longer tenable. Doctors Sinatra and Bowden provide all of us with a persuasive, fact-based interpretation and vision of the true role of cholesterol in cardiovascular illnesses.”

—MARK HOUSTON M.D., M.S., F.A.C.P., F.A.H.A., F.A.S.H., F.A.C.N., director, Hypertension Institute, Saint Thomas Hospital, Nashville, TN, and author of *What Your Doctor May Not Tell You About Heart Disease*

“The Great Cholesterol Myth is a remarkable book that will revolutionize the way in which heart disease is prevented, detected, and treated in this country.”

—ANN LOUISE GITTLEMAN, PH.D., C.N.S., best-selling author of *The Fat Flush Plan*

“This book clearly explains the tragic and harmful cholesterol and statin myths, and gives readers insight into those factors that really do promote a healthy heart.”

—PETER H. LANGSJOEN, M.D., F.A.C.C., founding member, Executive Committee, International CoEnzyme Q₁₀ Association

“Full of useful facts, backed up by the research literature, this book is entertaining and accessible to just about anybody who cares about their health. A must-read for those who are worried about their cholesterol levels and on the fence with statin therapy.”

—STEPHANIE SENEFF, B.S., M.S., E.E., PH.D., senior research scientist,
Massachusetts Institute of Technology

“Increasingly, doctors are questioning assertions that cholesterol is responsible for arterial disease, and that effective management requires lowering of cholesterol levels, especially with statins. At the same time, the noxious properties of the latter are being appreciated. It is therefore timely that Bowden and Sinatra provide this very readable explanation of why they think the way they do. Many readers will be persuaded.”

—HYWEL DAVIES, M.D., F.R.C.P., F.A.C.P., F.A.C.C., former chief of cardiology at
the Denver VA Hospital

“[The authors] demonstrate with compelling logic backed by scientific studies that doctors are doing more harm than good by prescribing statins as if they were after-dinner mints, with the false hope that a lower cholesterol level will prevent heart disease when underlying inflammation and oxidative stress are the real root causes of heart disease.”

—TODD LEPINE, M.D., The UltraWellness Center

“Dr. Bowden and Dr. Sinatra do an outstanding job providing a deep dive into all the causes of heart disease, while clarifying the role cholesterol plays. I would encourage this book to be required reading for all health science students, nutritionists, and physicians who treat patients!”

—COLETTE HEIMOWITZ, M.SC., vice president of nutrition and education,
Atkins Nutritionals, Inc.

“If you’re concerned about your cholesterol level and are thinking of taking a statin drug, this book is a must-read! It will change the way you think about heart disease—and it may save your life!”

—PRUDENCE HALL, M.D., founder and medical director, The Hall Center

“Be ready to be surprised, entertained, and to become healthy.”

—LARRY MCCLEARY, M.D., best-selling author of *Feed Your Brain, Lose Your Belly*

“This book is well written with excellent scientific references and from extremely knowledgeable authors. Read this book so you can be armed with the knowledge you need to make an informed decision before you treat your high cholesterol!”

—JENNIFER LANDA, M.D., chief medical officer of BodyLogicMD, author of *The Sex Drive Solution for Women*

“Jonny Bowden and Stephen Sinatra set the record straight on decades of bad science [and] put forth a far better solution about the true culprits that rob you of longevity: processed carbohydrates, insufficient vegetables, excess omega 6, and too many trans fats. Masterly, readable, and life-altering.”

—SARA GOTTFRIED, M.D., author of *The Hormone Cure*

“The authors have done their homework, and rather than rotely ‘following the leader’ they have dug into the extensive research and correlated it with their wide clinical experience to reveal the truth. This book can save many lives, including your own!”

—HYLA CASS, M.D., author of *8 Weeks to Vibrant Health*

“Thanks to the extensive scientific evidence provided by Bowden and Sinatra, the truth about cholesterol will hopefully end the utter madness that has plagued our society for far too long. Don’t even think about taking another statin drug, cutting your fat and cholesterol intake, or other ‘heart-healthy’ measures until you read *The Great Cholesterol Myth*. ”

—JIMMY MOORE, author of *Living ‘La Vida Low Carb* and *A Patient’s Guide to Understanding Your Cholesterol Test Results*

“This powerful new book will help the cholesterol test get the rest it deserves.”

—ALAN CHRISTIANSON, N.M.D., co-author, *The Complete Idiot's Guide to Thyroid Disease*

“If you want to know the truth about cholesterol, and what you absolutely must do to improve your heart health, this is the book for you. Jonny Bowden and Dr. Stephen Sinatra reveal the facts in a compelling and insightful way. This invaluable book belongs on the bookshelf of anyone who cares about the truth in medicine and healing.”

—DANIEL AMEN, M.D., CEO, Amen Clinics, Inc., author of *Use Your Brain to Change Your Age*

“Got high cholesterol or heart disease? Get this book!”

—JACOB TEITELBAUM, M.D., author of *Beat Sugar Addiction Now!* and *From Fatigued to Fantastic!*

“Finally! This timely book, written by the eminently qualified dream team of Dr. Jonny Bowden and Dr. Stephen Sinatra, exposes and unravels the great American cholesterol scam. Statin drugs sell in the U.S. for over \$30 billion per year, but do they really prevent heart disease? No! This must-read book will tell you how to really prevent heart disease and live a longer, healthier, leaner, fuller life.”

—DEAN RAFFELOCK, D.C., DIPL.AC., D.A.A.I.M., D.I.B.A.K., D.A.C.B.N., C.C.N., author of *A Natural Guide to Pregnancy and Postpartum Health*

“The book you’re holding is dangerous, and may even upset you. That’s because everything you know about cholesterol is probably wrong. Doctors Jonny Bowden and Stephen Sinatra provide both the science to vindicate this unfairly demonized molecule and a plan of action so you can attain optimal health.”

—JJ VIRGIN, best-selling author of *The Virgin Diet*

THE GREAT CHOLESTEROL MYTH

**WHY LOWERING YOUR CHOLESTEROL
WON'T PREVENT HEART DISEASE—
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JB:

To Robert Crayhon, who taught me about nutrition.

To Anja Christy, who taught me everything else.

And to Michelle, who teaches me every day what it is to truly love.

SS:

To my daughter, Marchann, who is the publisher of
www.heartmdinstitute.com, my website.

You have assisted me enormously in getting the truth out about integrative medicine. You are a dedicated patient advocate seeking out the truth in a sea of camouflage. I'm so blessed to have you in my life.

Love, Dad

“Never underestimate the convictions of the conventional, particularly in medicine.”

—William Davis, M.D.

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“The mind is like a parachute—it only works if it’s open.”

—Anthony J. D’Angelo

FOREWORD

TWO HUNDRED YEARS AGO physicians routinely bled, purged, and plastered their patients. Bloodletting was the standard treatment for a host of diseases and had been so since the time of the philosopher-physician Galen almost 2,000 years before. The theory was that there were four humors—blood, phlegm, black bile, and yellow bile. Blood was dominant, requiring the most balancing for returning an ill patient to health.

Every doctor's kit was equipped with a variety of lancets, brutal-looking scarificators, and, starting in the early nineteenth century, leeches. In fact, the latter were used so often that physicians were themselves commonly referred to as leeches. Learned physicians conferred on the best veins to tap for given diseases and the optimal placement of leeches for the most therapeutic value, and countless protocols dictated the proper amount of blood to be let or number of leeches to be applied. Doctors wrote lengthy papers describing their own bleeding techniques and presented them at august medical conferences.

The whole idea was nonsense, of course, and has been shown to be so in the early 1600s by William Harvey, the discoverer of how the circulatory system actually works. But the fact that the “scientific” basis for bloodletting was nonexistent didn't give pause to physicians 200 years ago, some of whom applied as many as fifty leeches to a single patient and, in the case of George Washington, relieved him of almost two quarts of blood in an effort to treat the throat infection that, coupled with the physician-caused anemia, ultimately killed him.

We look back today and can only shake our heads. And be thankful we, ourselves, don't have to worry about getting bled by lancet or leech or that with today's modern, truly science-based medicine, we would ever be exposed to such nebulously grounded treatments. Surely with all the scientific studies performed in great institutions the world over, today's doctors would never ignore the actual evidence and pursue unnecessary and possibly even harmful treatments. Would they?

Sadly, many doctors today have the same herd mentality as those doctors of yore. By the tens of thousands, they treat a nonexistent disease with drugs that are far from benign. And they do so based not on any hard scientific data, but because they, like their colleagues of 200 years ago, are firmly in the grip of group think. What is the nonexistent disease? Elevated cholesterol.

Cholesterol is an essential molecule without which there would be no life, so important that virtually every cell in the body is capable of synthesizing it.

The vast majority of laypeople have been bombarded with so much misinformation about cholesterol that most take it as a given that cholesterol is a bad thing and that the less they have the better. The reality is that nothing could be further from the truth.

Cholesterol is an essential molecule without which there would be no life, so important that virtually every cell in the body is capable of synthesizing it. Among its other duties, cholesterol is a major structural molecule, a framework on which other critical substances are made. Were we able to somehow remove all its cholesterol, the body, would, in the words of Shakespeare, “melt, thaw and resolve itself into a dew.” And that’s not to mention that we wouldn’t have bile acids, vitamin D, or steroid hormones (including sex hormones), all of which are cholesterol-based.

Despite the essential nature of cholesterol, doctors the world over administer billions of dollars’ worth of drugs to try to prevent its natural synthesis. The fact that only a tiny minority of patients actually extend their lives by taking these drugs is lost on the multitude prescribing them, but not, of course, on the pharmaceutical industry making and selling them. How did we come to this sorry state?

Sixty years ago a researcher, little known outside of academic circles, singlehandedly set us on this path of cholesterol paranoia: Ancel Keys, Ph.D., a proponent of what has become known as the lipid hypothesis,

concluded that excess cholesterol caused heart disease. He started out thinking that dietary fat in general drove cholesterol levels up, but as the years went by, he came to believe that saturated fat was the true cholesterol-raising villain. (This idea of saturated fat as villain is so ingrained in the minds of health writers that the words “saturated fat” are almost never written alone but always as “artery-clogging saturated fat.”) Which is more or less the basis for the lipid hypothesis: saturated fat runs up cholesterol levels, and elevated cholesterol leads to heart disease. Nice and simple, but not true. It has never been proven, which is why it is still called the lipid *hypothesis*.

Because of Keys’s influence, researchers for the past five decades have been beaver away in labs the world over, desperate to find enough actual proof to convert the lipid hypothesis into the lipid fact. But so far, they’ve fallen way short. In the process, however, they have vastly expanded our knowledge of the biochemistry and physiology of the cholesterol molecule. Thanks to their efforts, we now know that cholesterol is transported in the blood attached to carrier proteins, and that these protein-cholesterol complexes are called lipoproteins. Their densities now describe these lipoproteins: HDL (high-density lipoprotein), LDL (low-density lipoprotein), VLDL (very-low-density lipoprotein), and a number of others. Some of these lipoproteins are considered good (HDL) and others bad (LDL). And, of course, the drug companies have developed medications purported to increase the former while decreasing the latter.

But they jumped the gun. Researchers have discovered a type of lipoprotein called small, dense (or type B) LDL that may actually end up being a true risk factor for heart disease. Problem is, this small, dense type B LDL is worsened by the very diet those promoting the lipid hypothesis have hailed for decades as the best diet to prevent heart disease: the low-fat, high-carbohydrate diet. Turns out that fat, especially saturated fat, decreases the amount of these small, dense LDL particles while the widely recommended low-fat diet increases their number. The opposite of the small dense LDL are large fluffy LDL particles, which are not only *not* harmful but are actually healthful. But the LDL-lowering drugs lower those, too.

Cracks should have appeared in the firm entrenchment of the lipid hypothesis (that now basically posits that elevated LDL causes heart disease) when a recent study showed that of almost 140,000 patients

admitted to the hospital for heart disease, almost half of them had LDL levels *under* 100 mg/dL (100 mg/dL has been the therapeutic target for LDL for the past few years). Instead of stepping back, scratching their heads, and thinking, *Hmmm, maybe we're on the wrong track here*, the authors of this study concluded that maybe a therapeutic level of 100 mg/dL for LDL is still too high and needs to be even lower. Such is their lipophobic herd mentality.

Nutritionist Jonny Bowden, Ph.D., and cardiologist Stephen Sinatra, M.D., have teamed up in this book to slash through the tall thicket of misinformation surrounding cholesterol, lipoproteins, and the lipid hypothesis. They wrote their fact-based book using easy-to-understand terminology, and present a much more valid hypothesis of what really causes heart disease and a host of other diseases such as diabetes, high blood pressure, and obesity, that will open your eyes to the emperor's state of undress. If you are worried about your cholesterol level or contemplating taking a cholesterol-lowering drug, we urge you to read this book! This book will put the facts in your hands to make a more informed decision. And we're confident you will enjoy their book as much as we did.

Michael R. Eades, M.D.
Mary Dan Eades, M.D.
May 2012
Incline Village, Nevada

CHAPTER 1

WHY YOU SHOULD BE SKEPTICAL OF CHOLESTEROL AS AN INDICATOR OF HEART DISEASE

THE TWO OF US CAME TOGETHER TO WRITE THIS BOOK because we believe that you have been completely misled, misinformed, and in some cases, directly lied to about cholesterol.

We believe that a weird admixture of misinformation, scientifically questionable studies, corporate greed, and deceptive marketing has conspired to create one of the most indestructible and damaging myths in medical history: that cholesterol causes heart disease.

The millions of marketing dollars spent on perpetuating this myth have successfully kept us focused on a relatively minor character in the heart disease story, and created a market for cholesterol-lowering drugs worth more than \$30 billion a year. The real tragedy is that by putting all of our attention on cholesterol, we've virtually ignored the *real* causes of heart disease: inflammation, oxidation, sugar, and stress.

In fact, as you'll learn in this book, cholesterol numbers are a pretty poor predictor of heart disease; more than half the people hospitalized with heart attacks have perfectly normal cholesterol levels, and about half the people with elevated cholesterol levels have perfectly normal, healthy tickers.

Many of the general dietary guidelines accepted and promoted by the government and by major health organizations such as the American Heart Association are either directly or indirectly related to cholesterol phobia. These standard guidelines warn us to limit the amount of cholesterol we eat,

despite the fact that for at least 95 percent of the population, cholesterol in the *diet* has virtually no effect on cholesterol in the *blood*.

These guidelines warn us of the dangers of saturated fat, despite the fact that the relationship between saturated fat in the diet and heart disease has never been convincingly demonstrated, and despite the fact that research shows that replacing saturated fat in the diet with carbohydrates actually *increases* the risk for heart disease.

Both of us became skeptical of the cholesterol theory at different points in our careers, traveling different pathways to arrive at the same conclusion: Cholesterol does not cause heart disease.

We also believe that, unlike trans fat, for example, saturated fat is *not* the dietary equivalent of Satan's spawn (and we'll show you why). Finally, and most important, we strongly believe that our national obsession with lowering cholesterol has come at a considerable price. Cholesterolmania has caused us to focus all our energy around a fairly innocuous molecule with a marginal relationship to heart disease, while ignoring the *real* causes of heart disease.

We're each going to tell you in our own words how we became cholesterol skeptics and why we fervently believe the information contained in this book could save your life.

◀ WHAT YOU NEED TO KNOW

- Cholesterol is a minor player in heart disease.
- Cholesterol levels are a poor predictor of heart attacks.
- Half the people with heart disease have normal cholesterol.
- Half the people with elevated cholesterol have healthy hearts.
- Lowering cholesterol has extremely limited benefits.

DR. JONNY

Before I became a nutritionist and ultimately an author, I was a personal trainer. I worked at Equinox Fitness Clubs in New York City, and the vast majority of my clients were there for one thing: to lose weight. It was 1990. Fat was considered dietary enemy number one, and saturated fat was considered *especially* bad because we all “knew” it clogged your arteries, raised your cholesterol, and led to heart disease. So, like most trainers, I put my clients on low-fat diets and encouraged them to do a ton of aerobics plus a little bit of weight training.

Which worked.

Sometimes.

More often than not, the strategy bombed.

Take Al, for example. Al was an incredibly successful, powerful businessman in his early sixties with a huge belly he just couldn’t get rid of. He was eating a very low-fat diet, doing a ton of aerobics on the treadmill in his house, and yet his weight was hardly budging. If everything I had been taught as a personal trainer was right, that shouldn’t have been happening.

But it was.

Then Al decided to do something I didn’t approve of. He went on the Atkins diet.

Remember, those were the days when all of us were taught that fat, especially saturated fat, was pure evil. We had been taught that we “need” carbohydrates for energy and survival (we don’t, but that’s a discussion for another book). We had been taught that high-protein diets such as the Atkins diet were dangerous and damaging, largely because all that saturated fat would clog your arteries, raise your cholesterol, and lead to a heart attack.

So I was pretty sure Al was headed for disaster.

Except he wasn’t.

Not only did he start shedding weight and losing his substantial “apple-shaped” belly, but he also had more energy and was feeling better than he had in decades. I, meanwhile, was impressed with Al’s results, but I was

convinced he was paying a huge price and that once he got the blood test results from his annual physical, I would be vindicated.

I wasn't.

Al's triglycerides—a type of fat found in the bloodstream and elsewhere—had dropped, his blood pressure had gone down, and his cholesterol had risen slightly, but his “good” cholesterol (HDL) had gone up more than his “bad” cholesterol (LDL), so overall his doc was pretty happy.

Right around this time, a biochemist named Barry Sears came to New York City to give a workshop at Equinox, which, of course, I eagerly attended. Sears, whose Zone diet books have sold millions, had a novel approach that can be summed up in four words: *eat fat, lose weight*. (If Sears had been anything but an MIT-trained biochemist, he probably would have been laughed out of the room. But given his credentials and remarkable knowledge of the human body, he was pretty hard to dismiss.)

Now Sears wasn't the first one to embrace fat and protein in the diet and recommend that we eat fewer carbs. Atkins, whose original diet was the one Al had tried so successfully, had been saying similar things since 1972. But the whole rap against Atkins was that his diet was high in saturated fat and would therefore likely cause heart disease. So even though many people grudgingly admitted that you could lose weight easily following his program, everyone (including me) believed that the cost would include a hugely increased risk for heart disease.

What if the whole theory that cholesterol causes heart disease was wrong in the first place?

Meanwhile, my eyes were telling me something very different, and it wasn't just because of what I had seen happen with Al. It was happening with other clients as well. Sick of not getting results on low-fat, high-carb diets, they threw caution to the wind and embraced the Atkins diet and the Protein Power diet and other protein- and fat-friendly diets. They were eating more fat—even more saturated fat—but nothing bad was happening

at all, unless, of course, you count feeling better and getting slimmer as nothing.

Which got me thinking.

Why weren't we seeing consistent results with our clients who were faithfully following low-fat diets and getting plenty of aerobic exercise? Conversely, why were our clients who were going on low-carb diets getting such high marks on their blood tests and astonishing their doctors? What if everything we'd been told about the danger of saturated fat wasn't exactly correct? And—if what we'd been taught about saturated fat wasn't the complete truth—what about this relationship between fat and cholesterol? Was it really all as simple as I'd been taught?

After all, even back in the early '90s when people only talked about “good” and “bad” cholesterol, it was still obvious that, overall, saturated fat had a positive effect on Al's cholesterol, as it did on the cholesterol levels of so many of my other clients. Saturated fat raised their HDL much more than it did their LDL. Could this whole cholesterol issue be a little more complicated than I and everyone else had previously believed?

Eventually, I thought—going way out on a limb here—what if the whole theory that cholesterol causes heart disease was wrong in the first place? If that were the case, the effect of saturated fat on cholesterol would be pretty much irrelevant, wouldn't it?

Then I began reading the studies.

The Lyon Diet Heart Study¹ found that certain dietary and lifestyle changes were able to reduce deaths by 70 percent and reduce cardiovascular deaths by an even more impressive 76 percent, all without making as much as a dent in cholesterol levels. The Nurses' Health Study² found that 82 percent of coronary events were attributable to five factors, none of which had anything to do with lowering cholesterol. And that was just the tip of the evergrowing iceberg.

Contrary to what everyone thought, study after study on high-protein, low-carb diets, including those rich in saturated fat, showed that the blood tests of people on these diets were similar to Al's. Their health actually *improved* on these diets. Triglycerides went down. Other measures that indicated heart disease risk also improved.

In the mid-‘90s I went back to school for nutrition, ultimately earning a C.N. (certified nutritionist) designation and later a Ph.D. in holistic nutrition and a C.N.S. (certified nutrition specialist) certification from the Certification Board for Nutrition Specialists, which is associated with the American College of Nutrition. During my studies, I learned that I wasn’t the only one questioning the links among saturated fat, cholesterol, and heart disease. I talked to many other health professionals who shared my concerns, including one of the top lipid biochemists in the country, Mary Enig, Ph.D., whose entire academic career has been spent studying fat and who believes that we have nothing to fear whatsoever from saturated fat. (Enig, by the way, did some of the early research on trans fats and fervently believes that it is trans fats, not saturated fats, that are the real villains in the American diet; I wholeheartedly agree.)

Enig is hardly alone in thinking that we have been collectively brainwashed on the subject of saturated fat and cholesterol. She has pointed out that when Americans were consuming whole, full-fat foods such as cream, butter, pasture-raised meats, raw milk, and other traditional foods, the rate of heart disease was a fraction of what it is now. She had wondered aloud, as so many have since, whether it was indeed a coincidence that the twin global pandemics of obesity and diabetes just happened to occur around the time we collectively banished these foods because of the phobia about cholesterol and saturated fat in the diet and began to replace them with vegetable oils, processed carbs, and, ultimately, trans fats.

Enig was very active in a group for which I have come to have great respect: The Weston A. Price Foundation. Named after a pioneering researcher in the fields of diet and health, the foundation is an outspoken advocate for “traditional” unprocessed foods, including butter, raw milk, grass-fed meat, and other foods that have been demonized by the cholesterol establishment because of their relatively high saturated fat content. The foundation has also called much-needed attention to the fact that when Americans ate these foods regularly—for example, in the early part of the twentieth century—heart disease was much less common than it is now.

In my career, I have examined the strategies that seemed to work for the healthiest, longest-living people on earth and found that lowering cholesterol has almost *nothing* to do with reducing heart disease, and

definitely nothing to do with extending life. Study after study, including the Lyon Diet Heart Study, mentioned above, has shown that lowering the risk for heart disease has just about nothing to do with lowering cholesterol.

And more and more studies and reports were coming out demonstrating that the real initiators of damage in the arteries were oxidation and inflammation, with cholesterol more or less in the role of innocent bystander. Oxidation and inflammation, along with sugar and stress (more on that in [chapters 4](#) and [8](#)), were clearly what aged the human body the most. It seemed to me then—and it seems to me even more now—that *these* were the culprits we should be focused on, not on a fairly innocent molecule that is utterly essential to human health.

One of the greatest frustrations I experienced was trying to reassure my clients that not only would they not die if they went on higher-protein, higher-fat diets, but they'd also see significant improvements in their weights and the health of their hearts.

By now, I was pretty convinced that we had been massively misled about the role of cholesterol in heart disease, and we had been misled about the dangers of saturated fat as well. One of the greatest frustrations I experienced during this time was trying to reassure my clients that not only would they not die if they went on higher-protein, higher-fat diets, but they'd also see significant improvements in their weights and the health of their hearts. But I was constantly butting heads with my clients' doctors, who completely bought into the myth that saturated fat will kill you by clogging your arteries, raising your cholesterol, and ultimately leading to heart disease.

Fast-forward to 2010.

In 2010, Fair Winds Press—my publisher for thirteen books over the course of seven years—came to me with an idea. “How about a book on

how to lower cholesterol with food and supplements?” they asked.

To which I replied, “I’m probably not the guy to write that one. I don’t think lowering cholesterol matters very much.”

As you can imagine, that was met with a collective startle. My publishers were more than a little curious. “How can lowering cholesterol *not* be important?” they wanted to know. “Don’t doctors believe high cholesterol is the cause of heart disease? Don’t they believe that lowering it is the most important thing you can do when it comes to preventing heart attacks?”

“They do indeed,” I replied, “and they’re wrong.”

Intrigued, my publishers asked me for more information. I suggested they start by exploring the website of The International Network of Cholesterol Skeptics, www.thincs.org. I sent them a number of peer-reviewed studies that cast doubt on the relationship between saturated fat and heart disease. And I sent them the impeccable investigative work of award-winning science writer Gary Taubes, whose exhaustive investigations of the role of fat in heart disease (beginning with his seminal *New York Times* article, “What If It’s All Been a Big Fat Lie?”) has been so instrumental in calling attention to the profound weaknesses in the saturated fat–cholesterol–heart disease connection.

My friend Steve Sinatra is not only a board-certified cardiologist but also a trained psychotherapist and nutritionist. Like me, he’s also a member of the American College of Nutrition. And Steve has long believed that we’ve been sold a bill of goods on cholesterol. The story of how he came to the same conclusion that I did is fascinating and includes his own personal experience as a lecturer/educator for some of the biggest pharmaceutical companies on earth.

Steve promoted statin drugs and fully bought into the cholesterol-causes-heart-disease mythology that both of us have since abandoned.

Listen to his story in his own words, and you will begin to appreciate why we are both so passionate about revealing the truth about cholesterol and heart disease.

DR. SINATRA

Most doctors today will recommend that you take a statin drug—they might even nag you to do so—if your cholesterol numbers are high. They will do so whether or not you have evidence of arterial disease and are a man or woman, and despite your age. In their minds, you prevent heart disease by lowering cholesterol.

Once upon a time I used to believe that, too. It made sense, based on the research and information that was promoted to doctors. I believed it to the extent that I even lectured on behalf of drug makers. I was a paid consultant to some of the biggest manufacturers of statin drugs, lecturing for hefty honorariums. I became a cholesterol choirboy, singing the refrain of high cholesterol as the big, bad villain of heart disease. Beat it down with a drug, and you cut your risks. My thinking changed years ago when I began seeing conflicting evidence among my own patients. I saw, for instance, many patients with low total cholesterol—as low as 150 mg/dL!—develop heart disease.

In those days we pushed patients to undergo angiograms (invasive arterial catheterization imaging) if they had sufficient symptoms of chest pain, borderline exercise tests, and especially cholesterol readings of greater than 280 mg/dL. We did this because our profession believed that all people with high cholesterol were in danger of having a heart attack.

We did the imaging to see how bad their arteries were. And, indeed, sometimes we found diseased arteries. But just as often we didn't. Many arteries were perfectly healthy. These results were telling me something different than the establishment message—that it wasn't just a simple cholesterol story.

Faced with these discrepancies I began questioning and investigating conventional thinking about cholesterol and looking at the cholesterol research more closely. I found other doctors who had made similar discoveries on their own and heard about how study findings were being manipulated. For example, biochemist George Mann, M.D., of Vanderbilt University, who participated in the development of the world-famous Framingham Heart Study, later described the cholesterol-as-an-indicator-of-

heart-disease hypothesis as “the greatest scam ever perpetrated on the American public.”

These and other dissenting voices were drowned out by the cholesterol chorus. To this day, practically all of what has been published—and receives media attention—supports the cholesterol paradigm and appears to have the backing of the pharmaceutical and low-fat industries along with leading regulatory agencies and medical organizations.

However, I stopped being a choirboy for cholesterol. I stopped believing. Here’s why:

I found that life can’t go on without cholesterol, a basic raw material made by your liver, brain, and almost every cell in your body. Enzymes convert it into vitamin D, steroid hormones (such as our sex hormones—estrogen, progesterone, and testosterone—and stress hormones), and bile salts for digesting and absorbing fats. It makes up a major part of the membranes surrounding cells and the structures within them.

The brain is particularly rich in cholesterol and accounts for about a quarter of all the cholesterol we have in our bodies. The fatty myelin sheath that coats every nerve cell and fiber is about one-fifth cholesterol. Neuronal communication depends on cholesterol. It is not surprising that a connection has been found between naturally occurring cholesterol and mental function. Lower levels are linked to poorer cognitive performance.

I remember one patient—a federal judge I’ll call Silvio—who came to see me. He was taking a statin drug and complained that his memory had gone to pot, so much so that he voluntarily took himself off the bench. His LDL level was down to 65 mg/dL. I took him off the statin, told him to eat a lot of organic, cholesterol-rich eggs, and within a month got his LDL level up above 100 mg/dL. His memory came roaring back. (Memory loss is one potential side effect of cholesterol-lowering drugs.)

Some researchers suggest that doctors should be extremely cautious about prescribing statin drugs to the elderly, particularly those who are frail. I totally agree. I have seen frail individuals become even frailer and much more prone to infections. Though that surprised me at the time, it no longer does. Cholesterol plays a big role in helping fight bacteria and infections. A study that included 100,000 healthy participants in San Francisco over a

fifteen-year period found that those with low cholesterol values were much more likely to be admitted to hospitals with infectious diseases.³

Life can't go on without cholesterol, a basic raw material made by your liver, brain, and almost every cell in your body.

Many such patients told me afterward that their strength, energy, appetite, and vitality returned after going off statin drugs. They obviously needed their cholesterol.

In addition to being a board-certified cardiologist, I've had a lifelong interest in nutrition. I'd been using nutritional supplements in my practice since the early 1980s, particularly coenzyme Q₁₀ (CoQ₁₀), an absolutely vital nutrient that is made in every cell in the body and is a major chemical participant in the production of cellular energy. CoQ₁₀ is critically important for the strong pumping action of the heart, which gobbles the stuff up. And in the early '90s I discovered something that shook my belief in statin drugs to the core—they depleted the body of CoQ₁₀.

That fact is widely known now, but it wasn't then. And it certainly gave me pause. How could these miracle drugs that were believed to be the answer to heart disease be good for you in the long run if they depleted the very nutrient upon which the heart depends?

Even today, many doctors aren't aware of the effect that statin drugs have on CoQ₁₀ levels. How ironic that the very drug they prescribe to reduce the likelihood of a heart attack actually deprives the heart of the fuel it needs to perform properly? No wonder fatigue, low energy, and muscle pain are such frequent accompaniments to statin drug use.

It wasn't until the mid-1990s that statin drugs really took off, but prior to then physicians had other go-to drugs for lowering cholesterol. Many research studies were conducted using these drugs, and in 1996 the U.S. Government Accountability Office evaluated these trials in a publication titled *Cholesterol Treatment: A Review of the Clinical Trials Evidence*. The

report explained that though some trials showed a reduction in cardiovascular-related deaths (primarily among those who entered the studies with existing heart disease), there was a corresponding *increase* in *non*-cardiovascular-related deaths across the trials. “This finding, that cholesterol treatment has not lowered the number of deaths overall, has been worrisome to many researchers and is at the core of much of the controversy on cholesterol policy,” the authors wrote.

It was also quite clear from the report that those who benefited the most from lowering their cholesterol levels were middle-aged men who already had heart disease. “The trials focused predominantly on middle-aged white men considered to be at high risk of coronary heart disease,” the report stated. “They provide very little information on women, minority men and women, and elderly men and women.”

It’s been more than a decade since that report was written, but it remains true that lowering cholesterol has a very limited benefit in populations other than middle-aged men with a history of heart disease. Yet doctors continue to prescribe statin drugs for women and the elderly, and, shockingly, many are arguing for treating children with statins as well.

Lowering cholesterol has a very limited benefit in populations other than middle-aged men with a history of heart disease.

By now my conversion from cholesterol true believer to cholesterol skeptic is complete. I still prescribe statins—but only on occasion, and almost exclusively to middle-aged men who’ve already had a first heart attack, coronary intervention (e.g., bypass, stent, angioplasty), or coronary artery disease.

I’ve come to believe that cholesterol is a minor player in the development of heart disease and that whatever good statin drugs accomplish has very little to do with their cholesterol-lowering ability. (We discuss this at great length in [chapter 6](#), “The Statin Scam.”) Statin drugs are anti-inflammatory, and their power to reduce inflammation is much

more important than their ability to lower cholesterol. But we can lower inflammation (and the risk for heart disease) with natural supplements, a better diet, and lifestyle changes such as managing stress. Best of all, none of these come with the growing laundry list of troubling symptoms and side effects associated with statin drugs and cholesterol lowering.

LIKE DEAD MEN WALKING

So there you have it. Two individuals with very different journeys arriving at the same conclusion. And because that conclusion may be pretty hard to swallow if you've been brainwashed by the cholesterol establishment—and who hasn't?—it might be helpful to take a moment and talk about a study we alluded to earlier—the Lyon Diet Heart Study.

In the early 1990s, French researchers decided to run an experiment—known as the Lyon Diet Heart Study—to test the effect of different diets on heart disease.⁴

They took 605 men and women who were prime candidates for heart attacks. These folks had every risk factor imaginable. All of them had already survived a first heart attack. Their cholesterol levels were through the roof, they smoked, they ate junk food, they didn't exercise, and they had high levels of stress. People like this give insurance underwriters nightmares. To be frank, these folks were “dead men walking.”

The researchers divided the participants into two groups. The first group was counseled (by the research cardiologist and the dietician during a one-hour session) to eat a Mediterranean-type diet which emphasizes fresh fruit and vegetables, whole grains, legumes, nuts, healthy fats like olive oil, and seafood. The second group was the control group and received no dietary advice from the investigators but was advised, nonetheless, to follow a *prudent diet* by their attending physicians.

What was this prudent diet, you ask? Pretty much the standard (and, as we shall see, useless) diet that doctors have been recommending for decades: Eat no more than 30 percent of your calories from fat, no more than 10 percent from saturated fat, and no more than 300 mg of cholesterol a day (about the amount in two eggs). So what happened with the study?

Actually, it was stopped.

Why? Because the reduction in heart attacks in the Mediterranean diet group was so pronounced that the researchers decided it was unethical to continue. To be precise, the Mediterranean diet group had a whopping 70 percent reduction in deaths and an even more impressive 76 percent reduction in cardiovascular deaths. What's more, angina, pulmonary

embolism, heart failure, and stroke were also much lower in the intervention group. A huge victory for the Mediterranean diet and a big dunkin' for the prudent diet.

So what happened to these folks' cholesterol levels? Gosh, you'd imagine they dropped like crazy, because so few of them were dying of heart disease.

Um, not so much.

Their cholesterol levels *didn't budge*.

Let's repeat that one more time: a 76 percent reduction in deaths from heart disease but not a whit of change in cholesterol levels. Neither in their *total* cholesterol levels *nor* in their levels of LDL (the so-called "bad" cholesterol). You'd think this would shake up the cholesterol establishment a bit, wouldn't you?

Think again. The prestigious *New England Journal of Medicine* refused to publish the study. (It was eventually published in another highly regarded medical journal, *The Lancet*.) We have a hunch that the reason the *New England Journal of Medicine* didn't publish the study was precisely because there was no difference in cholesterol levels between the two groups of people, the ones who did so well and the ones who did not. The American medical establishment is so firmly locked into the notion that cholesterol and fat cause heart disease that any inconvenient evidence to the contrary—and there is a massive amount of it, as you will soon find out—has to be ignored or explained away.

Lower heart disease rates? And no movement in cholesterol numbers?

Something has to be wrong!

Actually something *was* wrong, but not with the study. What was—and is—wrong is the blind belief that cholesterol simply makes a huge difference.

An Inconvenient Fact

Not convinced? Fast-forward to a drug study completed in 2006, the widely publicized ENHANCE trial.⁵ If you were following the news in 2008 you couldn't have missed this one, because it made the front pages of the newspapers and all of the television news shows. Here's what happened.

A combination cholesterol-lowering medication called Vytorin had been the subject of a huge research project, the results of which were finally coming to light and receiving an enormous amount of negative attention. One of the many reasons for this negative attention was the fact that the companies jointly making the drug (Merck and Schering-Plough, who've since merged) waited almost two years before releasing it.

No wonder. The results stunk. Which was the *other* reason this drug test made the front pages.

The new “wonder” drug lowered cholesterol just fine. In fact, it lowered it *better* than a standard statin drug. So you'd think everyone would be jumping for joy, right? Lower cholesterol, lower heart disease, let's have a party for the shareholders.

Um, not quite. Although the people taking Vytorin saw their cholesterol levels plummet, they actually had *more* plaque growth than the people taking the standard cholesterol drug. The patients on Vytorin had almost twice as great an increase in the thickness of their arterial walls, a result you definitely don't want to see if you're trying to prevent heart disease.

So their cholesterol was wonderfully lowered and their risk for heart disease went up—shades of “the operation was a success but the patient died.”

There are countless other examples, many of which we'll discuss later on, but let's just mention one of them right now. It's known as the Nurses' Health Study, and it's one of the longest-running studies of diet and disease ever undertaken. Conducted by Harvard University, the study has followed more than 120,000 females since the mid-1970s to determine risk factors for cancer and heart disease.⁶ In an exhaustive analysis of 84,129 of these women, published in the *New England Journal of Medicine*,⁷ five factors were identified that significantly lowered the risk for heart disease. In fact, wrote the authors, “Eighty-two percent of coronary events in the study . . . could be attributed to lack of adherence to (these five factors).”

Are you ready for the five factors?

1. Don't smoke.
2. Drink alcohol in moderation.

3. Engage in moderate-to-vigorous exercise for at least half an hour a day on average.
4. Maintain a healthy weight (BMI under 25).
5. Eat a wholesome, low-glycemic (low-sugar) diet with plenty of omega-3 fats and fiber.

Wait, didn't they miss something? Where's the part about lowering cholesterol?

Oh. It's not there. Never mind.

Of course, there's not roughly \$30 billion plus a year to be made peddling that advice (a number that represents the gross revenue from statin drugs alone), and popping a pill is a lot easier than changing your lifestyle, but there it is. The inconvenient fact that lowering cholesterol has almost *no effect* on extending life is simply ignored by the special interests that profit enormously from keeping you in the dark.

As the writer Upton Sinclair said, "It is very difficult to get a man to understand something, when his salary depends upon his not understanding it."

CHAPTER 2

“CHOLESTEROL IS HARMLESS!”

NOW LET’S TALK ABOUT YOU FOR A MOMENT.

Unless you’re just an information junkie, there’s a good chance that you’re reading this book because you have something at stake here. Let us guess: You’re concerned about *your* cholesterol.

Maybe you’re a woman whose doctor has read you the riot act because your cholesterol is approaching 300 mg/dL, and your doc has convinced you that you’ll drop dead of a heart attack if you don’t go on medication right away.

Maybe you’re a middle-aged man who has already had a heart attack, and your doctor is adamant about putting you on a cholesterol-lowering drug.

Or maybe you’re a fit guy in your sixties whose cholesterol is 240 mg/dL and whose doctor is “worried” about that number.

However, only *one* of the three hypothetical cases listed above has any business being on a cholesterol-lowering drug. Can you guess which one? Don’t worry: By the time you finish this book, you’ll not only know the answer, you’ll also know a heck of a lot more about cholesterol than most doctors in America. And, no, we don’t make that statement lightly.

CHOLESTEROL BASICS

Cholesterol is a waxy substance—technically a *sterol*—that is an important constituent of cell membranes. The vast majority of cholesterol in the body is made in the liver, while the rest is absorbed from the diet.

Cholesterol is the basic raw material that your body uses to make vitamin D; sex hormones such as estrogen, progesterone, and testosterone; and the bile acids needed for digestion. Cholesterol travels in particles called lipoproteins, the most common of which are high-density lipoproteins (HDL) and low-density lipoproteins (LDL).

Below we address the long-held, conventional views on cholesterol basics that we believe to be outdated.

WHAT IS HDL?

Old School

HDL is considered “good” cholesterol because it helps remove so-called “bad” cholesterol, LDL. When measured, HDL levels should be as high as possible, preferably 60 milligrams per deciliter of blood (mg/dL) and above. Maintaining a healthy weight, physical activity, and a diet that includes healthy fats like olive oil are believed to keep HDL levels high.

New School

HDL is much more tightly controlled by genetics than LDL. A 2011 study from the National Institutes of Health, AIM-HIGH, found that raising HDL did nothing to protect against heart attacks, strokes, or death. And all HDL is not the same. HDL-2 particles are large and buoyant and the most protective. HDL-3 particles, on the other hand, are small and dense and may be inflammatory. HDL-2 is anti-inflammatory and anti-atherogenic (atherosclerosis being the condition in which an artery wall thickens from the accumulation of fatty materials, called plaque, induced by inflammation, inhibiting blood flow from the heart). HDL-3, on the other hand, is poorly understood. You want to have higher levels of HDL-2 than HDL-3.

The “New School” generally agrees that higher levels of HDL are desirable, but research is concentrating on the *function* of HDL subtypes rather than the total amount. Daniel Rader, M.D., director of preventive cardiology at the University of Pennsylvania, wrote in the *New England Journal of Medicine*, “Recent scientific findings have directed increasing interest toward the concept that measures of the function of HDL, rather than simply its level in the blood, might be more important to assessing cardiovascular risk and evaluating new HDL-targeting therapies.”

WHAT IS LDL?

Old School

LDL is “bad” cholesterol because it can build up in the arteries, impeding blood flow. Its levels should be kept low. Current standards are 100 to 129 mg/dL, with lower than 100 being the target for those at risk for heart disease, and lower than 70 being the target for people at very high risk. Too much saturated fat in the diet, inactivity, and being overweight are considered to raise LDL levels.

New School

All LDL is not the same. LDL-A is a buoyant, fluffy molecule that does no harm whatsoever as long as it is not damaged by oxidation (a process caused by free radicals that enables cholesterol to form plaque). LDL-B is a small, hard, dense, molecule that promotes atherosclerosis. A pattern of high LDL-A is the most beneficial. Blood tests today can also measure the number of LDL-A and LDL-B particles.

The most important cholesterol particle of all, which conventional tests do not focus on, is Lp(a). Lp(a) is a very small, highly inflammatory particle that is thrombogenic (blood clotting). Dr. Sinatra calls it “the alpha wolf” of cholesterol particles. In a healthy body, low Lp(a) levels aren’t much of a problem. Lp(a) circulates and carries out repair and restoration work on damaged blood vessels. However, the more repairs you need on your arteries, the more Lp(a) is utilized. Lp(a) concentrates at the site of damage, binds with a couple of amino acids within the wall of a damaged blood vessel, dumps its LDL cargo, and

starts to promote the deposition of oxidized LDL into the wall, leading to more inflammation and ultimately to plaque.

Also, Lp(a) promotes the formation of blood clots on top of the newly formed plaque, which narrows the blood vessels further.

HOW CHOLESTEROL IS MEASURED

Old School

A standard blood test will tell you your total cholesterol level and your HDL and LDL levels.

New School

Measure cholesterol with the newer particle tests, which tell you how much of your LDL is type A and how much of your LDL is type B (see [chapter 9](#) for more information). Measure the *number* of actual particles, and the amount of the potentially dangerous Lp(a). That is the only information that matters.

DIETARY ADVICE

Old School

Eat less 300 mg of cholesterol a day and eat less than 10 percent of calories as saturated fat.

New School

According to the Framingham Heart Study, people who consumed the most cholesterol in their diets did not have any higher blood cholesterol levels than those who consumed the least amount. The effect of dietary cholesterol on blood (serum) cholesterol is very variable and individual, and for most people—though not all—the effect of dietary cholesterol on serum cholesterol is insignificant.

In any case, because cholesterol is not as an important risk factor for heart disease as once believed, it doesn't matter very much. Saturated fat raises cholesterol, but it raises overall HDL cholesterol and the *good* part of LDL cholesterol (LDL-A) far more than it raises the bad part of LDL cholesterol (LDL-B). There is no evidence that supports a *direct* relationship between saturated fat and heart disease.

RELATIONSHIP TO HEART DISEASE

Old School

High levels of cholesterol are an important risk factor for heart disease because cholesterol builds up in the arteries, inhibiting blood flow from the heart.

New School

Cholesterol is a relatively minor player in heart disease and a poor predictor of heart attacks. More than half of all people who are hospitalized with heart attacks have perfectly normal cholesterol levels.

When the National Cholesterol Education Program lowered the “optimal” cholesterol levels in 2004, eight out of nine people on the panel had financial ties to the pharmaceutical industry.

Besides the fact that you’re concerned about your cholesterol, there are two other things we can assume. One, you don’t tend to blindly follow recommendations without doing your own research. (If you did, you’d simply be following your doctor’s orders and have no interest in reading this book.)

The second thing we’re pretty sure about you is that you’re smarter than the average reader.

Here’s why:

To understand the cholesterol myth—and to fully appreciate how the health advice that follows from the myth is obsolete—you’ll need to know a lot more about cholesterol than the average person knows. But reading—and understanding—the full story of cholesterol, including the myths, misconceptions, outright lies, and misguided medical practices, doesn’t

make for easy reading. It'll take quite a bit more intelligence, motivation, and perseverance than, say, reading the latest romance paperback.

The cholesterol story touches on not only medicine and research but also politics, economics, psychology, and sociology. It's got a cast of characters ranging from the obnoxious and egotistical to the well-meaning and misguided.

It has heroes and villains, mavericks and traditionalists, all engaged in a battle that, sadly, has little to do with saving lives (though it may have started out that way). It involves staggering amounts of money, the politics of publication, the sociology of belief (why bad ideas continue to survive past their expiration dates), and the revolving door that exists between government advisory committees and the industries they're supposed to police. (Example: When the National Cholesterol Education Program lowered the "optimal" cholesterol levels in 2004, eight out of nine people on the panel had financial ties to the pharmaceutical industry, most of them to the manufacturers of cholesterol-lowering drugs who would subsequently reap immediate benefits from these same recommendations.)

By now it should be pretty clear that neither of us buys into the myth that cholesterol is the proper target for the prevention of heart disease. But how did the myth get started in the first place? How, exactly, did cholesterol and saturated fat come to be branded as the twin demons of heart disease?

To answer that question, we need to go back to 1953, when a young, ambitious biologist named Ancel Keys proposed the then-radical theory that heart disease was caused by too much fat in the diet.

THE BIRTH OF THE DIET–HEART HYPOTHESIS

It's hard to imagine that this theory was radical given how widespread its acceptance is today, but at the time the prevailing wisdom was that diet had little to do with heart disease. But Keys felt he was on to something.

Previous research by Russian scientists had shown that when you fed rabbits large amounts of cholesterol and then dissected them later on, their arteries were filled with cholesterol-containing plaque and looked suspiciously like the arteries of people who died of heart disease. Never mind the inconvenient fact that rabbits are herbivores. The amount of cholesterol they normally get in their diets is pretty close to zero. Other animals, such as rats and baboons, do *not* react in the same way as rabbits to a high-cholesterol diet, and they metabolize cholesterol very differently. Even Keys himself understood that cholesterol in the diet was of no importance. In 1997, he stated, “There’s no connection whatsoever between cholesterol in food and cholesterol in blood. And we’ve known that all along. Cholesterol in the diet doesn’t matter at all unless you happen to be a chicken or a rabbit.”

Yet the admonition to eat “no more than 300 mg of cholesterol” a day remains the advice of every major health organization to this day, despite the fact that even the scientist most responsible for popularizing the diet–heart hypothesis thought it was ridiculous.

Inconvenient facts to the contrary, excess cholesterol in the *blood*, not the diet, seemed to Keys to be a likely culprit in the development of heart disease.

Since fat in the diet and cholesterol in the blood were believed to be linked, this led Keys to investigate fat in the diet and its connection to heart disease. He looked at data on fat consumption and heart disease from various countries and published the results of his famous study, the Seven Countries Study, which supposedly demonstrated a clear link between the amount of dietary fat consumed and the incidence of heart disease. Those countries eating the most fat also had the highest rates of heart disease. Sounds like an open-and-shut case against dietary fat, doesn’t it?

Except it was anything but. When Keys published the results of his study, he actually had available to him reliable food consumption data from twenty-two countries, but he used only seven. By hand-selecting the seven countries that supported his preconceived hypothesis, Keys was able to make a convincing case that there was a direct connection between dietary fat and heart disease.

The fact that Keys had chosen to include only seven countries and ignored the other fifteen didn't exactly go unnoticed. Many researchers criticized Keys for conveniently omitting data that didn't support his theory. Researchers analyzing the data from all twenty-two countries found that the correlation between fat, cholesterol, and heart disease literally vanished.

One of the researchers who questioned Keys was a British doctor named John Yudkin from the University of London. He found that there were countries where the intake of fat was virtually the same, but the rates of cardiovascular disease were vastly different. For example, Finland was one of the countries used by Keys to make his case, because Finland had a high per capita fat intake and a high rate of heart disease. But Yudkin found that the people of West Germany ate the exact same amount of fat as the people of Finland, but they had about one-third the rate of heart disease. The paradox was even more pronounced in the Netherlands and Switzerland, which also had only one-third the rate of heart disease seen in Finland, even though the Dutch and Swedes consumed even *more* fat than the Finns.

Yudkin's much more comprehensive data showed that the single dietary factor that had the strongest association with coronary heart disease was—wait for it—*sugar*.

Yudkin did a far more extensive analysis of dietary factors than Keys did. He looked at fat as a percentage of calories. He looked at different types of fats. He even looked at the roles of carbohydrates and protein. And instead of confirming Keys's hypothesis, Yudkin's much more

comprehensive data showed that the single dietary factor that had the strongest association with coronary heart disease was—wait for it—*sugar*.

So back to Keys. By all accounts, Keys was a very smart and well-liked man who just happened to be dead wrong on the cholesterol and fat issue. But he was hardly without ambition and ego. Known for being blunt and biting, he presented his theory on fat, cholesterol, and heart disease to a distinguished audience in 1954, when the World Health Organization (WHO) held its first expert committee on the pathogenesis of atherosclerosis. One of his longtime collaborators, Henry Blackburn, recalled that Keys was stunned to find that his ideas were not accepted on the spot. One participant asked him to cite the principle piece of evidence for his diet–heart theory, and he was caught, to put it mildly, off guard. “Ancel fell into a trap, he made a mistake,” Blackburn said. “He cited a piece of evidence, and they were able to destroy it. He got up from being knocked to the ground and went out saying, ‘I’ll show those guys,’ and designed the Seven Countries Study.”³

The Seven Countries Study⁴ is actually the cornerstone of current cholesterol and fat recommendations and official government policy, so it’s worth looking at in some detail. Keys examined saturated fat consumption in seven countries, and, lo and behold, he found a straight-line relationship between heart disease, cholesterol levels, and saturated fat intake—exactly what he had hoped to find.

The seven countries were Italy, Greece, the former Yugoslavia, the Netherlands, Finland, the United States, and Japan. It hardly went unnoticed that Keys chose only the countries that fit his hypothesis. He easily could have chosen a different group of countries and proven a completely different hypothesis.

In fact, British physician Malcolm Kendrick, M.D., did exactly that. Kendrick used the same data available to Keys and quickly discovered that if you simply chose different countries, you could easily prove that the *more* saturated fat and cholesterol people consumed, the *lower* their risk of heart disease.⁵

Anticipating a challenge to his “proof” by defenders of the cholesterol hypothesis, Kendrick pointed out that he was merely doing exactly what Keys did—hand-selecting data that would prove his theory. “What do you

mean I can't choose my own countries?" he asked sarcastically. "That's not fair. Keys did!"⁶

Cherry-picking the countries that proved this theory was only one of the many problems with the Seven Countries Study. There were tremendous variations in heart mortality within these countries, even though saturated fat consumption was identical. In Finland, for example, the intake of saturated fat was almost identical in two population groups from Turku and North Karelia. But heart mortality was three times higher in North Karelia. Similarly, saturated fat intake was also equal on two Greek islands, Crete and Corfu. But heart mortality was a whopping seventeen times higher on Corfu than it was on Crete.⁷

How did Keys explain these facts, which were clearly present in his data?

Simple. He ignored them.

Keys was a member of the nutrition advisory committee of the American Heart Association, so despite the flaws in his study, he managed to get his theories officially incorporated into the 1961 American Heart Association dietary guidelines,⁸ where they have influenced government policy on heart disease, fat consumption, and cholesterol for decades.

At the time, Keys's theories about fat and cholesterol weren't exactly widely known outside scientific circles, and the whole theoretical fight between the advocates of the "sugar" hypothesis and the advocates of the "fat" hypothesis was all so much ivory-tower name-calling, well out of the earshot of the general public. But all that was about to change.

And the man who was indirectly responsible for that change was, interestingly, not a scientist at all but a politician named George McGovern.

The Politics of Science

McGovern, chairman of the Senate Select Committee on Nutrition and Human Needs, practically changed the national policy on nutrition in this country. And they were directly responsible for transforming the idea that dietary fat causes heart disease from a not-so-solid hypothesis into solidified dogma.

McGovern's committee instituted a wonderful series of landmark federal food assistance programs, but its work on malnutrition started to wind down

around the mid-1970s. McGovern's committee staffers, notably its general counsel, Marshall Matz, and staff director, Alan Stone, both lawyers, decided to go for broke and take on the reverse side of the malnutrition coin: *overnutrition*. "It was a casual endeavor," Matz said. "We really were totally naive, a bunch of kids who just thought, 'Hell, we should say something on this subject before we go out of business.'"⁹

The committee listened to two days of expert testimony in 1976 and then assigned a young writer named Nick Mottern to write the whole thing up. The only problem was that Mottern didn't know anything about nutrition and health and had no science writing background to boot. So he did what any smart young writer would do: He went to the experts for guidance.

◀ WHAT YOU NEED TO KNOW

- The theory that fat and cholesterol cause heart disease became widely accepted *despite* much evidence to the contrary. This evidence deserves to be reexamined. The case needs to be reopened.
- Many doctors did *not* agree with the cholesterol myth and questioned the science upon which it was based.
- The studies upon which the cholesterol myth was based were later found to be problematic.
- The adoption of the cholesterol myth by mainstream organizations and the government had a strong political component to it.

Except in this case, Mottern didn't actually go to the "experts"; he went to one *particular* expert, Mark Hegsted, a Harvard nutritionist, and relied almost exclusively on Hegsted's interpretation of the testimony, as well as on Hegsted's own personal recommendations.

Hegsted was a fervent believer in the emerging theory that low-fat diets would prevent heart disease and that fat and cholesterol were the spawn of Satan.

Whoops.

So Mottern wrote up the committee's recommendations with Hegsted as the final authority—no more than 30 percent of calories from fat, no more than 10 percent of calories from saturated fat—and in 1977 the committee disbanded. But right around that time, a newly appointed assistant secretary at the U.S. Department of Agriculture (USDA) named Carol Tucker Foreman decided that the USDA ought to *do* something with these recommendations. Like make them official policy! The only problem was that she needed some good scientific cover.

Fair enough. Foreman wasn't a scientist herself, but she sure had access to some good ones. So she went to the president of the National Academy of Sciences (NAS), Philip Handler, a distinguished expert in human metabolism.

Want to know what he told her?

The anti-fat dietary goals written by Mottern were utter and complete nonsense.

Well.

So Foreman did what other good officials would do when they don't like the advice they're getting. She went to someone else.

Can you guess whom she went to?

Hegsted. The champion of the low-fat, low-cholesterol eating plan who had practically written the guidelines in the first place.

Not surprisingly, Hegsted had an entirely different opinion from Handler. With cover from Hegsted, the USDA was able to release *Using the Dietary Guidelines for Americans*, a low-fat, low-cholesterol manifesto that echoed exactly the same anti-fat, anti-cholesterol sentiments written in the original Mottern–Hegsted document put out by the McGovern committee.

What happened next makes the backstabbing antics of the television show *Survivor* look like child's play.

The National Academy of Sciences Food and Nutrition Board, not happy with the USDA report, issued its own set of guidelines titled *Toward Healthful Diets*. Here's the *Reader's Digest* condensed version of what it said: "Don't worry about fat."

This pretty much directly contradicted the report of the USDA, which had recommended very specific fat intakes: less than 30 percent of total

calories from fat and less than 10 percent from saturated fat.

The USDA didn't take this slap in the face sitting down and leaked reports to the press saying that the chairman of the NAS Food and Nutrition Board and one of the board's members had financial ties to the food industry, as if this were enough to explain why the board as a whole didn't endorse the USDA recommendations to avoid fat. The beef and dairy industries went nuts and lobbied with all their might against the recommendations, calling them unjustified by science. But the die had been cast. In the current political climate, the "fat cat" cattle ranchers reminded folks of the tobacco industry, which had responded in much the same way when cigarettes first came under attack. Meanwhile, the grain lobbyists, as you can imagine, were in heaven.

The media had a field day, and they were not kind to the NAS. Mainstream apologist Jane Brody, who has written about food and nutrition for the *New York Times* for decades, accused the NAS board members of being "all in the pockets of the industries being hurt."¹⁰ And because everyone on both sides of the argument had enormous amounts of money at stake, the debate between the beef industry and the grain industry was hardly a model of scientific objectivity. It was far more about image and public relations: The fat cat ranchers were portrayed as peddling unhealthy, "high-fat," "artery-clogging" foods, while the grain farmers were seen as the "good guys," on the side of science, health, granola, and the well-being of the American people. High-carb, low-fat cereals became the new health food, while high-fat meats were seen as poison, peddled by greedy cattle ranchers indifferent to the health of America. Basically, the anti-fat movement didn't evolve out of science at all, but instead was a grassroots movement fueled by a distrust of the "establishment"—Big Food, Big Medicine, and Big Ranchers. It was also fueled by the countercultural bias against excessive consumption, represented in this case by big, fatty steaks and bacon and eggs.

We all know who won that public relations battle.

Think it's a coincidence that the obesity and diabetes epidemics went into overdrive around the same time that we started pushing low-fat, high-carb diets as an alternative to those containing more fat and protein? We don't.

The Snackwell Phenomenon

Low-fat had become the new mantra of the times, something we like to call the "Snackwell Phenomenon." Food companies rushed to create low-fat versions of every food imaginable, all marketed as "heart-healthy," with no cholesterol. (No one seemed to notice that manufacturers *replaced* the missing fat with tons of sugar and processed carbs, both of which are far more dangerous to our hearts than fat ever was.)

Butter was demonized and replaced with margarine, one of the most supremely stupid nutritional swap-outs in recent memory. Only much later did we discover that the supposedly healthier margarine was laden with trans fats, a really bad kind of fat created by using a kind of turkey baster to inject hydrogen atoms into a liquid (unsaturated) fat, making it more solid and giving it a longer shelf life. (Any time you read "partially hydrogenated oil" or "hydrogenated oil" in a list of ingredients, that means the food in question contains trans fats.) Unlike saturated fats from whole foods such as butter, trans fats (at least the manmade kind) actually *do* increase the risk for heart disease and strokes!

About 80 percent of trans fats in the American diet come from factory-produced partially hydrogenated vegetable oil.¹¹ Yet vegetable oils were (and are!) aggressively promoted as the healthy alternative to saturated fats, even though most of these oils are highly processed, pro-inflammatory, and easily damaged when reheated over and over again, which is standard procedure in many restaurants.

Think it's a coincidence that the obesity and diabetes epidemics went into overdrive around the same time that we started pushing low-fat, high-

carb diets as an alternative to those containing more fat and protein? We don't.

But by now, fat—and, by extension, cholesterol—had become the new bogeyman of the American diet, defended only by people who clearly had a horse in the race (e.g., the dairy and meat industries), and low-fat had become the new religion of the masses. Now it was left for the science to catch up. The National Institutes of Health (NIH) funded half a dozen studies that were published between 1980 and 1984, hoping it would find persuasive evidence that low-fat diets prolonged lives.

Did they?

Not exactly.

Let's Go to the Videotape

The first four of these trials compared heart disease rates and diets in four locations: Honolulu, Puerto Rico, Chicago, and, most famously, Framingham, Massachusetts. Not *one* of these trials showed the slightest evidence that men who ate low-fat diets lived any longer, or had fewer heart attacks, than those who ate high-fat diets.

The fifth trial was the MRFIT study, a research project that cost \$115 million and involved twenty-eight medical centers and 250 researchers. In the MRFIT study, 360,000 men, aged thirty-five to fifty-seven, from eighteen different U.S. cities were screened between 1973 and 1977, and eventually about 13,000 middle-aged, healthy men who were considered especially prone to heart disease were selected to participate. These 13,000 men were randomly assigned to one of two groups. The control group received no special instructions about diet or lifestyle and just continued on with whatever general medical care they received from their doctors. The intervention group, however, was urged to avoid eating fat, to quit smoking, to exercise, and to lower their blood pressure.

After seven years of follow-up, the intervention group had slightly lower blood pressure and cholesterol than the control group, but there was *no difference* in either cardiovascular mortality or all-cause mortality (scientific lingo for “total number of deaths no matter what the reason”). The intervention group had 17.9 deaths per one thousand men from cardiovascular disease, and the control group had 19.3 deaths per one thousand

men, a variation that did not amount to what researchers call *statistical significance*, meaning it was likely due to chance.¹²

In addition, the data on overall mortality—death from any cause—was troubling. There were actually *more* deaths in the intervention group—from any cause—than there were in the control group! Remember, the real reason we want to avoid heart disease is so we can live longer; avoiding heart disease isn't much of a victory if it means you die early from some other disease!

The researchers themselves described the results as “disappointing.” The only *real* reduction in overall mortality was seen with the people who stopped smoking, regardless of the group they were in.¹³

Leaping to the Wrong Conclusion

The sixth of the NIH-funded trials, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), which was initiated in 1973, is worth mentioning because of an interesting leap of faith made by the investigators based on virtually no evidence. But this leap of faith became the cornerstone of anti-fat policy for decades to come. Here's what happened.

Researchers from the National Heart, Lung, and Blood Institute measured cholesterol in almost one-third of a million middle-aged men and chose only those with the highest cholesterol levels for the study (about 4,000 men). They gave half of them a new cholesterol-lowering drug (cholestyramine), while the other half got a placebo. The medicine did indeed lower cholesterol levels in the men who had abnormally high levels to begin with, and it modestly reduced heart disease rates in the process. (The probability of suffering a heart attack during the seven to eight years of the study went from 8.6 percent in the placebo group to 7 percent in the group treated with cholestyramine, while the probability of dying from a heart attack dropped from 2 to 1.6 percent, not exactly jaw-dropping numbers.¹⁶)

WHAT THE FRAMINGHAM HEART STUDY FOUND

One study mentioned most often by the defenders of the cholesterol theory is the Framingham Heart Study. This long-running research study started back in 1948 and monitored heart disease in more than 5,000 residents of Framingham, Massachusetts. After following up for sixteen years, the researchers claimed to find a direct correlation between heart disease and cholesterol levels.

But God is in the details. As it turned out, the group of Framingham residents who developed heart disease and the group of Framingham residents who didn't had similar ranges of cholesterol levels. In fact, the *average* cholesterol level of the heart disease group was only 11 percent higher than that of the group *without* heart disease. Cardiovascular disease struck people with cholesterol levels as low as 150 mg/dL. Low cholesterol, according to this study, was hardly a guarantee of a healthy heart.

It gets better (or worse, depending on your position). When researchers went back and looked at the Framingham data thirty years after the project started, they found that once men passed the age of forty-seven, it didn't make a whit of difference whether their cholesterol was low or high.¹⁴ Those with high cholesterol at age forty-eight lived just as long as, or *longer* than, those who have had low cholesterol. So if cholesterol is important only for the relatively few who have had a heart attack before the age of forty-eight, why are the rest of us worried about high-fat food and cholesterol levels?

The question is hardly academic. In 1992, forty-four years after the Framingham project began, study director William Castelli, M.D., wrote the following in an editorial in the *Archives of Internal Medicine*:

“In Framingham, Mass., the *more* saturated fat one ate, the *more* cholesterol one ate, the *more* calories one ate, the *lower* the person's serum cholesterol . . . we found that people who ate the *most* cholesterol, ate the *most* saturated fat, [and] ate the *most* calories weighed the least and were the most physically active [*italics ours*].”¹⁵

Okay, cholesterol goes down, heart disease drops by a thimble, and the researchers conclude that lowering cholesterol lowers the risk of heart disease. But remember, this was a *drug* trial, not a *diet* trial. The researchers made a huge leap of faith by assuming that if lowering cholesterol is “good” (i.e., it reduces the risk of heart disease), it shouldn’t much matter *how* you lower it. Lowering it through diet should get you the same “good” result (if you can call the miniscule drop in heart disease that may or may not be related to the drop in cholesterol a “good” result). Their leap of faith was that we should recommend low-fat diets because they will achieve the same result as the drug—cholesterol will go down and everyone will live happily ever after.

But drugs often have many effects in addition to their main purpose. (Remember, Viagra was originally designed as a blood pressure medication!) The drug used in the LRC-CPPT might also have had some good effects, such as lowering inflammation, for example. Assuming that lowering cholesterol with a low-fat diet was identical to lowering it with a multifaceted medication that could in fact have had unintended benefits was a complete leap of faith and led to the wholesale recommendation of a low-fat diet for the prevention of heart disease.

That same year, the NIH held what’s called a “consensus conference” to basically justify the LRC-CPPT and the dietary recommendations that came out of it, yet it was anything but a consensus. Several experts pointed to significant defects in the studies and even called into question their accuracy. But you’d never know it from the final report, which made it seem like everyone had unquestioningly hitched their collective stars to the low-fat bandwagon.

Well, not exactly everyone.

CONSENSUS? NOT EXACTLY

George Mann, M.D., associate professor of biochemistry at Vanderbilt University College of Medicine and a participating researcher in the Framingham Heart Study, was one of the doubters.

The diet–heart idea is the “greatest scam” in the history of medicine, he said. “[Researchers] have held repeated press conferences bragging about this cataclysmic breakthrough, which the study directors claim shows that lowering cholesterol lowers the frequency of coronary disease. They have manipulated the data to reach the wrong conclusions.”¹⁷

Mann also declared that NIH managers “used Madison Avenue hype to sell this failed trial in the way that media people sell an underarm deodorant!”¹⁸

Michael Oliver, a highly respected British cardiologist, concurred. “The panel of jurists . . . was selected to include experts who would, predictably, say that . . . all levels of blood cholesterol in the United States are too high and should be lowered. Of course, this is exactly what was said.”¹⁹

But the dissenting voices met with radio silence. With pompous certainty, the committee made clear in its final report that low-fat diets would afford significant protection against coronary heart disease for men, women, and children over two years old. “The evidence justifies . . . the reduction of calories from fat . . . to 30 percent, calories from saturated fat to 10 percent or less, and dietary cholesterol to no more than 250 to 300 mg daily,” it declared.²⁰

As Dr. Phil might ask, “And how’s that workin’ for you?”

One study that attempted to answer this hypothetical question was the Women’s Health Initiative, the same program that has suggested that hormone therapy after menopause has more risks than benefits. This \$415-million NIH study involved close to 49,000 people, aged fifty to seventy-nine, who were followed for eight years in an attempt to answer the question, “Does a low-fat diet reduce the risk of getting heart disease or cancer?”²¹

They got their answer.

“The largest study ever to ask whether a low-fat diet reduces the risk of getting cancer or heart disease has found that the diet has no effect,” the *New York Times* reported in 2006.²²

“These studies are revolutionary,” said Jules Hirsch, M.D., physician-in-chief emeritus at the Rockefeller University in New York City and an expert on how diets influence weight and health. The studies “should put a stop to this era of thinking that we have all the information we need to change the whole national diet and make everybody healthy.”²³

Of course, none of these questionable findings stopped the cholesterol-lowering, fat-avoiding juggernaut that went into full swing in the late 1970s and continues, albeit bruised and battered, to this day. And we have to give the misguided researchers kudos for their motives—by reducing cholesterol levels, they sincerely believed they would be reducing heart disease. As Dwight Lundell, M.D., author of *The Cure for Heart Disease*, wryly put it, “They were taking the bull by the horn—but it was the wrong bull.”²⁴

When we first met about this project, Steve brought to the meeting a series of papers by one of the most respected researchers in the world, Michel de Lorgeril, M.D., a French cardiologist and researcher at the prestigious National Centre for Scientific Research, the largest public organization for scientific research in France.

De Lorgeril has authored dozens of papers in peer-reviewed journals, and he was the lead researcher for the Lyon Diet Heart Study. The following quotation comes from his only book written in English, and it’s a perfect way to end this chapter:

“We can summarize . . . in one sentence: *Cholesterol is harmless* [italics ours]!”²⁵

CHAPTER 3

INFLAMMATION: THE TRUE CAUSE OF HEART DISEASE

SO IF CHOLESTEROL *ISN'T* THE CAUSE OF HEART DISEASE, what is?

We know you don't want to wait any longer, so here's the short answer: The primary cause of heart disease is *inflammation*.

The subject of inflammation will be a running theme throughout this book for reasons that will soon be made clear, but the first thing you need to know about inflammation is this: It comes in two flavors. You're probably already familiar with one of them, but it's the one you're *less* familiar with that's at the core of heart disease.

Let us explain.

Almost all of us have experience with *acute* inflammation. It happens every time you stub your toe, bang your knee, or get a splinter in your finger. When you complain about your aching back, an abscess in your mouth, or a rash on your skin, that's acute inflammation. It's visible and uncomfortable, if not downright painful. The redness on your skin is a result of blood that's rushed to the affected area. The swelling you experience is the result of an army of specialized cells (with names like *phagocytes* and *lymphocytes*) dispatched by the immune system to mend the injured area. (The job of these immune system cells is to surround the site of the injury and neutralize nasty invaders such as microbes, preventing the spread of potential infection.) The swelling, redness, and soreness you experience as a result of acute inflammation are all natural accompaniments to the healing process.

So we all know about acute inflammation, most of us from personal experience. But the *other* flavor of inflammation, *chronic* inflammation,

well, that's a whole different ball game.

Acute inflammation hurts, but chronic inflammation kills.

WHY YOU SHOULD CARE ABOUT CHRONIC INFLAMMATION, NOT CHOLESTEROL

Chronic inflammation flies beneath the pain radar. Much like high blood pressure, it has no obvious symptoms. Yet chronic inflammation is a significant component of virtually every single degenerative condition, including Alzheimer's, diabetes, obesity, arthritis, cancer, neurodegenerative diseases, chronic lower respiratory disease, influenza and pneumonia, chronic liver and kidney diseases, and, most especially, heart disease.

A BETTER WAY TO PREDICT HEART DISEASE

Want a much better way to tell whether you're at risk? Look at these two line items on your blood test: triglycerides and HDL (the so-called "good" cholesterol).

Now if you're not too freaked out about doing a bit of math, calculate the ratio of your triglycerides to your HDL. If, for example, your triglycerides are 150 mg/dL and your HDL is 50 mg/dL, you have a ratio of 3 (150:50). If your triglycerides are 100 mg/dL and your HDL is 50 mg/dL, you have a ratio of 2 (100:50).

This ratio is a far better predictor of heart disease than cholesterol ever was. In one study out of Harvard published in *Circulation*, a journal published by the American Heart Association, those who had the highest triglyceride-to-HDL ratios had a whopping sixteen times the risk of developing heart disease as those with the lowest ratios.¹ If you have a ratio of around 2, you should be happy, indeed, regardless of your cholesterol levels. (A ratio of 5, however, is problematic.)

When chronic inflammation exists unchecked in the cardiovascular system, it usually spells big trouble for the heart.

And inflammation is rarely a local phenomenon. For instance, women with rheumatoid arthritis, a highly inflammatory condition that primarily affects the joints, wind up having double the risk of a heart attack when compared to women without it. Microbes that cause problems in one part of the body can easily migrate to other areas and cause inflammatory damage there. An infection that starts in the gums, for example, can easily leak bacteria into the bloodstream, bacteria that may then find fertile ground in a weakened arterial wall and fan the fires of inflammation there.

So how exactly does inflammation happen, and, more importantly, what can we do about it?

OXIDATION: THE INITIATOR OF INFLAMMATION

In *The Most Effective Ways to Live Longer*, Dr. Jonny introduced the concept of the “Four Horsemen of Aging.” These Four Horsemen all contribute mightily to heart disease, and we’ll go over all of them in the pages that follow. For those of you who just have to know *right now* what they are, here’s the list: oxidation, inflammation, sugar, and stress. In this chapter, we’ll concentrate on the first two.

One of the prime initiators of inflammation is *oxidation*. If you’ve ever seen rust on metal, you’re familiar with oxidation (also known as *oxidative damage*), even if you didn’t know the technical name for it. You’re also familiar with oxidation if you’ve ever left apple slices out on a picnic table where they were exposed to the air. They turned brown, didn’t they? *That’s* oxidative damage.

For those of you who don’t remember high school chemistry (or would understandably prefer to forget it), electrons travel in pairs and orbit around atoms. Every so often one of those electrons gets “loose,” and pandemonium ensues. The unpaired electron—known as a *free radical*—starts running around like a headless chicken trying to find its head. Free radicals are like college sophomores on spring break—temporarily free from the constraints of dormitory living, they basically go nuts and will “mate” with anyone! Free radicals “hit” on existing, stable pairs of electrons thousands of times a day, trying to find an electron they can pair-bond with and meanwhile, inflicting enormous damage upon your cells and DNA.

The free radicals that come from oxygen (known, not surprisingly, as *oxygen free radicals*) are the most deadly and damaging. (Now you know what the term “*antioxidants*” means—it’s a class of substances, including certain vitamins, minerals, and many plant chemicals, that helps neutralize free radicals, soaking them up like little sponges, thus limiting the damage they can do to your body. The reason cut apple slices don’t turn brown so quickly when you squirt lemon juice on them is because lemon juice contains a fair amount of vitamin C, a powerful antioxidant.)

Free radicals are so important that in the mid-1950s a scientist named Denham Harman, M.D., Ph.D., put forth a theory called the Free Radical Theory of Aging that remains popular to this day.² In it he basically proposes that aging is a kind of “rusting from within,” largely due to the damage caused by oxygen free radicals.

Okay, hold that thought. We’re going to come back to it. But before we go any further, let’s look at the arteries, or more specifically the arterial walls, because that’s where the damage starts.

Ground Zero for Damage: Introducing the Endothelium

The arterial walls are anything but hard and firm. They’re composed of smooth muscle that expands and contracts like a mini accordion; they respond to the rhythm of the heart and accommodate the pulsing of the blood. These arteries—far from being a static system of tubes and pipes—are a living, breathing, *very* dynamic organ. And the innermost layer of the artery walls—the “interface,” if you will, between the blood inside the arteries and the walls that contain it—is a central player in our little drama. This layer is called the *endothelium*—and it’s the starting point for the damage that can ultimately lead to a heart attack.

Big word, endothelium, yes, not often bandied about in cocktail party chatter about heart disease, but it’s one of the most important places in the arteries for you to know about because *that’s* where the damage to your arteries starts. The endothelium is only one cell thick, but it’s where a tremendous amount of biochemical activity takes place. There’s even a name for the pathological state in which damage to that innermost layer exists—it’s called *endothelial dysfunction*, and it’s a key event in the development of heart disease.

◀ WHAT YOU NEED TO KNOW

- Cholesterol is the parent molecule for sex hormones (estrogen, progesterone, and testosterone) as well as vitamin D and bile acids needed for digestion.
- The only time cholesterol is a problem is if it's *oxidized* (damaged).
- Damaged or oxidized LDL cholesterol sticks to the lining of the arteries and begins the process of inflammation.
- The true cause of heart disease is inflammation.
- Inflammation is initiated by damage from free radicals (oxidative stress).
- The concept of “good” and “bad” cholesterol is outdated.
- There are several types of LDL (“bad”) cholesterol and several types of HDL (“good”) cholesterol.
- It is far more important to know whether you have a pattern A or pattern B LDL cholesterol profile than to know your total amount of LDLs.
- A cholesterol level of 160 mg/dL or less has been linked to depression, aggression, cerebral hemorrhages, and loss of sex drive.

FOR MEN ONLY

Note to the men reading this: Endothelial dysfunction has the same acronym (ED) as another condition you may be familiar with or concerned about: erectile dysfunction. They're not unrelated. Our friend Mark Houston, M.D., director of the Hypertension Institute and an associate professor of medicine at Vanderbilt University, wryly commented, "I've never seen a case of ED (erectile dysfunction) that didn't also have ED (endothelial dysfunction)."

Bottom line: A healthy functioning endothelium is essential for . . . more things than just the heart!

Okay, we've introduced two important concepts here—oxidative damage and inflammation—and one important structure—the endothelium. Now we need to take a look at what cholesterol is and see how it fits into the whole picture. Once we do, we will return to the interaction among oxidation, inflammation, and the arterial walls.

“GOOD” AND “BAD” CHOLESTEROL: A COMPLETELY OUTDATED CONCEPT

Contrary to cholesterol’s negative reputation, your body simply can’t function without it. It’s found in every single cell and is so essential that the lion’s share of the cholesterol in your body is actually *made* by your body, specifically by the liver, which produces this fatty, waxy substance precisely *because* it is so essential to the health of your cells.

The cholesterol you eat has a minimal effect on your blood levels of cholesterol, which is why the admonition to eat less of it and the prominent listing of cholesterol on food nutrition labels are not as significant as we are led to believe they are. If you eat *less* cholesterol, your liver will simply take up the slack and make more. If you eat *more* of it, the liver makes *less*. It is primarily, overwhelmingly made in the liver, though small amounts are made in other locations. For all intents and purposes, “manufacturing central” is the liver, and this is what responds to the “eat more/make less, eat less/make more” seesaw. The Framingham Heart Study found that there was virtually *no difference* in the amount of cholesterol consumed on a daily basis by those who went on to develop cardiovascular disease and those who did not. Egg-white omelet eaters, take note!

Cholesterol’s ability to fight toxins may be one reason why it’s found at the site of arterial injuries caused by inflammation. But blaming cholesterol for those injuries is a little like blaming firemen for fire.

As we said earlier, cholesterol is the basic raw material that your body makes into vitamin D; sex hormones such as estrogen, progesterone, and testosterone; and the bile acids needed for digestion. The emphasis on lowering cholesterol as much as possible is not only misguided but also dangerous. Studies show that those at the lowest end of the cholesterol

spectrum have a *significantly* increased risk of death from myriad conditions and situations unrelated to heart disease, including, but not limited to, cancer, suicide, and accidents.

Accidents and suicides? Really? Yes. Here's the connection: You need cholesterol to make brain cells. A cholesterol level too low (around 160 mg/dL) has, in fact, been linked to depression, aggression, and cerebral hemorrhages. (The connection to sex drive will be discussed later in [chapter 6](#)—it's a doosey!)

The membranes of your cells contain a ton of cholesterol because it helps maintain their integrity and also facilitates cellular communication. The consistency of the cell membrane has to be just right—hard enough to act as a barrier to all sorts of molecular riff-raff but pliable and soft enough to allow access to the molecules that need to get inside. Essentially, you *need* cholesterol for memory. Lower cholesterol too much and it can easily promote a kind of global amnesia; with too little cholesterol in the cell membranes, nerve transmission can be affected. It's no surprise to us that Duane Graveline, M.D.—a former flight surgeon and astronaut who received international recognition for his research on zero gravity deconditioning—gave his book about the memory loss he experienced after taking statin drugs the ominous title *Lipitor: Thief of Memory*.

Cholesterol is also one of the important weapons your body uses to fight infections. It helps neutralize toxins produced by bacteria that swarm into the bloodstream from the gut when the immune system is weakened. When you have an infection, the total blood level of cholesterol goes up, but HDL (which we'll define in a moment) falls because it's being used up in the fight. Cholesterol's ability to fight toxins may be one reason why it's found at the site of arterial injuries caused by inflammation. But blaming cholesterol for those injuries is a little like blaming firemen for the fire.

Now here's an interesting fact of which you might not have been aware: It's actually impossible to measure cholesterol directly in the bloodstream. Being a fatty substance, cholesterol is not soluble in water or blood. So how does it get in the bloodstream? Simple. Your liver coats it with a “protein wrapper” and bundles it with a few other substances (such as triglycerides); packaging it in this protective shell allows it to enter your circulatory system, much like stones would float in the ocean if they were contained in a buoyant, waterproof container. In our case, the protein wrapper acts like a

passport, allowing cholesterol to travel throughout your bloodstream. It's these packages, known as *lipoproteins*, that we actually measure when we measure our cholesterol levels.

We know these cholesterol–protein combinations as HDL (*high-density lipoprotein*) and LDL (*low-density lipoprotein*). Both contain cholesterol and triglycerides, but the percentages are different, and the two types of lipoproteins have different functions in the body. LDL, known as “bad” cholesterol, carries cholesterol to the cells that need it, while HDL, known as “good” cholesterol, picks up the excess and carries it back to the liver.

But this old idea of “good” and “bad” cholesterol is a wholly outdated concept.

We now know that there are many different “subtypes” of both HDL and LDL, and they do very different things. LDL, the imprecisely named “bad” cholesterol, has several different subtypes, and not all of them are bad at all—quite the contrary.

The most important subtypes of LDL are subtype A and subtype B. When most of your LDL is of the “A” type, you're said to have a *pattern A* cholesterol profile. When most of your LDL is of the “B” type, you're said to have a *pattern B* cholesterol profile. Simple, right? And absolutely essential to know for reasons soon to be made clear.

Subtype A is a big, fluffy molecule that looks like a cotton ball and does just about as much damage, which is to say none. Subtype B, however, is small, hard, and dense, like a BB gun pellet. It's the real bad actor in the system, because it's the one that becomes oxidized, sticks to the arterial walls, and starts the cascade of damage. Subtype B particles (what we might call the “bad” bad cholesterol) are atherogenic, meaning that they contribute significantly to heart disease. As we've already noted, big, fluffy LDL particles (the “good” bad cholesterol) are pretty much benign. Knowing you have a “high” LDL level is pretty much a useless piece of information *unless* you know how *much* of that LDL is the small, dense kind (harmful) and how much is the big, fluffy kind (not harmful in the least). Both of us would be totally comfortable having a high LDL number if the bulk of it was composed of the big, harmless, cotton ball–type molecules (the pattern A distribution). That's much more preferable than having a *lower* LDL number mostly composed of the BB gun pellet–type molecules (the pattern B distribution).

Unfortunately, most doctors are behind the times on this one. They look at that total LDL number—not the size and type—and if that number is even slightly higher than the lab says it should be, out comes the prescription pad. Pharmaceutical companies love when advisory committees—which are often heavily stacked with doctors who have financial ties to the pharmaceutical companies—recommend that we maintain lower and lower LDL levels, because that means a bigger and bigger market for cholesterol-lowering drugs. Sadly, most doctors do not perform the easily available tests—often covered by insurance—that determine your LDL.

You may recall from the first chapter that present-day health recommendations to reduce cholesterol by any means possible started with the Framingham Heart Study. In 1948, when the study began, cholesterol was only measured as “total” cholesterol. If you knew what your cholesterol was, you knew one specific number (200 mg/dL or 220 mg/dL, for example). As recently as 1961 we didn’t have the technology to distinguish between “good” and “bad” cholesterol (HDL and LDL), much less the newer technology that allows us to zero in on different subtypes of the so-called “bad” cholesterol, which, as you can see, is far from being all “bad” after all.

Even HDL, the so-called “good” cholesterol, isn’t *all* good. A study published in the December 2008 issue of the *FASEB Journal*, produced by the Federation of American Societies for Experimental Biology, challenged the conventional wisdom that simply having high levels of good cholesterol (HDL) and low levels of bad cholesterol (LDL) is necessary for good health. The researchers showed that even *good* cholesterol has varying degrees of quality and that *some* HDL cholesterol is actually bad news.

“For many years, HDL has been viewed as good cholesterol and has generated a false perception that the more HDL in the blood, the better,” said the lead researcher, Angelo Scanu, M.D., of the University of Chicago.³ “It is now apparent that subjects with high HDL levels are not necessarily protected from heart problems and should ask their doctors to find out whether their HDL is good or bad.” Scanu’s study found that the HDL of people with chronic diseases such as rheumatoid arthritis and diabetes is very different than the HDL of healthy individuals, even when

their blood levels of HDL are similar. Normal, “good” HDL cholesterol reduces inflammation; dysfunctional, “bad” HDL does not.

Knowing you have a “high” LDL level is pretty much a useless piece of information unless you know *how much* of that LDL is the small, dense kind (harmful) and how much is the big, fluffy kind (not harmful in the least).

THE GOOD, THE BAD, AND THE REALLY, REALLY UGLY!

This just in: As of this writing, new research funded by the British Heart Foundation has uncovered still another subtype of LDL cholesterol that is particularly bad. It’s called the *MGmin-low-density lipoprotein*, and it’s more common in people with type 2 diabetes and in the elderly. It’s “stickier” than normal LDL, which makes it much more likely to attach to the walls of the arteries.

This new “ultra-bad” boy is actually created by a process called glycation, which sharp-eyed readers will recall is one of the Four Horsemen of Aging. Glycation happens when there’s too much sugar hanging around in the bloodstream. The excess sugar starts gumming up the works, inserting itself in places where it doesn’t belong—in this case, the LDL molecule. (We’ll have a lot more to say about sugar and its role in heart disease later on in [chapter 4](#). Preview: Sugar is way more of a threat to your heart than fat ever was!)

“This is yet one more line of research that explains why some people can have perfect cholesterol levels, but still develop cardiovascular disease,” said Gerald Weissmann, M.D., editor-in-chief of the *FASEB Journal*. “Just as the discovery of good and bad cholesterol rewrote the book on

cholesterol management, the realization that some of the ‘good cholesterol’ is actually *bad* will do the same.”⁴

The point is that there is, indeed, “bad” cholesterol—even “*ultra*-bad” cholesterol—but simply using a shotgun pharmaceutical approach to lowering all cholesterol doesn’t accomplish anything and has significant unwanted side effects, as we will see in [chapter 6](#).

Now that the four main characters in our drama have been introduced—oxidation, inflammation, cholesterol, and the arterial walls—let’s see how they interact in real life, and how they work together to create a dangerous situation for your heart.

WHEN LDL *REALLY* IS BAD FOR YOU: THE SMOKER'S PARADOX

Here's a riddle for you: Why is it that smokers with *normal* LDL (the so-called “bad” cholesterol) levels have a much higher risk of heart disease than non-smokers with elevated LDL levels?

Sure, we all know how cigarette smoke damages the lungs, and that cigarette smoking significantly increases the odds of getting lung cancer. But, really, what's the connection between smoking and heart disease, or, more specifically, between smoking and LDL cholesterol?

Glad you asked.

Besides the harsh smoke, cigarettes also graciously provide your body with myriad toxic chemicals, all at no extra charge, thank you very much. These chemicals and toxins both constrict the blood vessels and harm the arterial walls. Specifically, they cause your LDL to become oxidized—damaged by the free radicals that are found in abundance in cigarette smoke! (And, by the way, it's not just cigarette smoke that can oxidize LDL. Heavy metals like mercury can do it, as can insecticides, radiation, and all manner of toxins in the environment, the air, and the food supply.)

And listen carefully now: LDL is *never* a problem in the body *until* it becomes oxidized. Only oxidized LDL sticks to the arterial walls, contributing to plaque and causing further inflammation and injury. Non-oxidized LDL is pretty much harmless. It's oxidation that actually initiates the process that culminates in atherosclerosis.

So a smoker with a low amount of LDL, *most* of which has been damaged by oxidation, is at far greater risk for heart disease than a nonsmoker with a much *higher* level of LDL, only a tiny percentage of which has been damaged. It's not the LDL that causes the problem—it's *damaged* (oxidized) LDL.

So LDL floats around in the bloodstream, delivering cholesterol to the cells that need it, and *some* of this LDL, the LDL that's damaged by oxidation, infiltrates the endothelium. Once the endothelium becomes infiltrated with this damaged LDL, the process of inflammation begins in earnest.

Remember our earlier discussion about harmless “bad” cholesterol (LDL pattern A) and dangerous “bad” cholesterol (LDL pattern B)? Well, one of the reasons why pattern B molecules (those BB gun–pellet types) are so bad is that they are the ones most likely to be damaged and most likely to be oxidized. On top of that, they’re small enough to penetrate the arterial walls in the first place. The smaller the particles (and pattern B particles are small indeed), the more inflammatory they are. Oxidized LDL is like “angry” LDL, and the smaller the particle, the angrier it is. So these nasty little damaged LDL particles stick to the endothelium and begin the process of inflammation. In the presence of oxidative damage—or in the presence of high blood sugar, which is such an important initiator of damage that we’ll examine it separately in [chapter 4](#)—this LDL experiences chemical changes that the immune system perceives as dangerous.

Once the immune system notices this damaged (oxidized) LDL, it sends in the heavy artillery. First, cells known as *monocytes* rush to the scene of the action, releasing chemicals called *cytokines*. Cytokines are essentially chemical messengers that help regulate the immune system response, but many of these cytokines are themselves highly inflammatory. In the presence of some of these cytokines, the lining of the blood vessels (the endothelium) secrete sticky little molecules called *adhesion molecules* that act like molecular glue, grabbing on to the monocytes that have rushed to the scene of the crime to help put out the fire. Heart surgeon Dwight Lundell, M.D., cleverly refers to this as the “Velcro effect.”

Monocytes now convert into a type of cell we like to call “Little Ms. Pac-Man.” They’re technically called *macrophages*, and their job, much like Ms. Pac-Man in the video game, is to eat up the enemy, in this case the damaged LDL particles and other molecular junk that have caused the problem in the first place. (The word *macrophage* literally means “big eater.”)

The macrophages are like sugar addicts at a pie-eating contest. They have no off button; they’ll keep eating, consuming oxidized LDL until they literally choke to death, leaving something called the *lipid core* of plaque. Once they reach a certain size they start to look like foam and actually become what pathologists call “foam cells,” living cells that will continue the work of the macrophages, fighting and consuming until the “invader” is gone.

But it isn't an invader that sets them off. It's just plain old LDL experiencing chemical changes from sugar, starches, or oxidation and thus initiating an inflammatory process that can easily become an out-of-control "fire" within your arterial walls. As we've said, without inflammation, it's pretty irrelevant what your cholesterol levels are.

If inflammation isn't halted and if macrophages continue to feast away until they bust, they'll release a whole new set of toxins into the walls of the artery.

"We can see this in surgery as a yellow streak inside the artery wall," said Lundell, who has performed more than five thousand heart surgeries. "It is called the 'fatty streak,' and it is the beginning of significant heart disease."⁵

The body tries to contain this fatty streak by building a wall to hold it in—scarring is an example. But the immune system is now on full alert; it sends more soldiers to the front, and they try valiantly to break down the wall (the scar tissue), and the cycle continues—more scarring, more soldiers. Over time, if the body's immune system defenses are good enough, they will weaken the wall of the artery and literally "chew through" the scar tissue. A rupture will occur, resulting in more inflammation, and the potentially deadly cycle continues.

Not good news.

If the cycle is not stopped, the fatty streak grows into what's known as plaque. (Plaque is basically a big old collection of foam cells.) Some foam cells will die, and they will release a whole bunch of the accumulated fats (lipids), which in turn develop into the aforementioned lipid core, a soft, yellowy substance that resembles melted butter (but isn't nearly as good for you).

Now if you stop the inflammation at this point in time, the artery heals itself with what's called a *fibrous cap*. The fibrous cap is composed of fibrous scar tissue and will stay nice and stable. (Cardiologists like Steve call this "stable plaque.") Of course, if there's new inflammation, the cycle begins all over again.

So the more inflammation continues, the more foam cells accumulate. This means more macrophages (Ms. Pac-Man), which in turn means more oozy, slimy *lipid core*. This lipid core gets into the bloodstream, where the

blood immediately puts out a signal saying, “What the heck is this? Foreign object! Foreign object!” And a blood clot is formed in an attempt to keep this foreign, gooey substance from spreading.

So the blood clot is actually a protective mechanism. It’s the blood’s—or the body’s, if you prefer—way of saying, “Let’s contain this threat and keep it from spreading!” But though this strategy makes sense, it has a big downside. That blood clot may block access to the heart muscle, preventing oxygen from getting through. Anytime you deprive cells of oxygen, the tissue they make begins to die.

And when that tissue is the muscle of the heart, you’re looking at—you guessed it—a heart attack.

So overall, LDL can be likened to trees in a forest. A forest that has tons of trees but gets plenty of rain isn’t likely to be the site of a wildfire, but a forest with far fewer trees can be a tinder box just waiting to ignite if all those trees are dried up (damaged) and there’s very little rainfall! Getting rid of the trees is surely *one* crude way to prevent forest fires, just as lowering cholesterol indiscriminately *might* theoretically decrease the risk of a “fire” in your artery walls, but at what cost? Those trees serve a lot of ecological purposes, and removing them is not without consequences, both to the environment and to the landscape.

Wouldn’t it be better to reduce the conditions under which a fire is likely to break out? That way we could have all the wonderful benefits of trees with none of the side effects of a compromised ecology.

We hope we’ve convinced you that inflammation is at the core of heart disease, and that it’s inflammation—and its main initiator, oxidation—we need to be concerned about, not cholesterol.

But oxidation is only one of the conditions—albeit a very important one—that causes inflammation.

Another cause of inflammation is so important we’re giving it its own chapter. It’s something you eat every day and something you already know is bad for you, but only because of its well-documented role in diabetes and obesity. What you’re about to learn is the connection between this common food and heart disease.

By the time you finish the next chapter, you’ll be convinced—as we are—that this food is a far, far greater danger to your overall health, and

specifically to your heart, than fat ever was.

We're talking about sugar.

CHAPTER 4

SUGAR: THE REAL DEMON IN THE DIET

FOR THOSE OF YOU WHO LIKE TO CUT RIGHT TO THE CHASE, here's this chapter's take-home point: Sugar is a far greater danger to your heart than fat ever was.

The full story of sugar, and of its often ignored influence on heart disease, requires that we venture into a topic we like to call Endocrinology 101. We understand this sounds like something an evil high school biology teacher designed for the express purpose of making your life miserable, but we promise not to make your eyes glaze over. In fact, by the time you finish this chapter, you will know more than many doctors do about the common link among heart disease, diabetes, obesity, and hypertension—conditions that are not exactly of casual interest to most readers.

Once you understand the link that joins all of these modern degenerative diseases and its connection to heart disease, we believe you'll come to the same conclusion we have: Our health gurus have tried and convicted the wrong man, your honor. Fat was innocent all the time.

It's *sugar* that's the true culprit in the American diet.

ENDOCRINOLOGY 101: THE HORMONAL EFFECT OF FOOD

Our journey starts with one simple premise: Hormones control almost every metabolic event that goes on in your body, and *you* control some of the most critical hormones through your lifestyle. Food—along with several key lifestyle factors such as stress—is the drug that stimulates hormones, and those hormones direct the body to store or burn fat, just as they direct the body to perform a gazillion other metabolic operations.

“Food may be the most powerful drug you will ever encounter because it causes dramatic changes in your hormones that are hundreds of times more powerful than any pharmaceutical,” said Barry Sears, Ph.D. Hormones are the air traffic controllers that determine the fate of whatever flies in (or in our case, “slides” in through the gullet!).

This fact has been conveniently ignored by many mainstream dietitians and doctors whose standard message to overweight people at increased risk for heart disease is to simply reduce calories and saturated fat. But all calories are not created equal. Some foods significantly boost levels of a hormone that *stores* fat, while other foods do not—even when the calories are the same. Not coincidentally, that fat-storing hormone also has some serious consequences for the heart.

The name of that fat-storing hormone? Insulin.

Insulin, a hormone first discovered in 1921, is the star actor in our little hormonal play. It is an anabolic hormone, which means it is responsible for building things up—putting compounds like glucose (sugar and amino acids) inside storage units (such as cells). Its sister hormone, glucagon, is responsible for breaking things down—opening those storage units and releasing their contents as needed. Insulin is responsible for *saving*; glucagon is responsible for *spending*. Together their main job is to maintain blood sugar levels within the tightly regulated range it needs to be to keep your metabolic machinery running smoothly.

Insulin is at the hub of a significant number of diseases of civilization. When you control insulin, you reduce the risk for not only heart disease but

also hypertension, diabetes, polycystic ovary syndrome, inflammatory diseases, and even, possibly, cancer.

Both insulin and glucagon are essential to health. Without insulin, blood sugar would skyrocket, and the result would be coma and death, the fate of virtually every type 1 diabetic in the early part of the twentieth century prior to the discovery of insulin. However, without glucagon, blood sugar would plummet, and the result would be brain dysfunction, coma, and death.

So the body knows what it's doing. This little dance between the force that keeps blood sugar from soaring too *high* (insulin) and the forces that prevent it from going too *low* (glucagon, for one) is essential for survival. It's interesting to note that although insulin is the only hormone responsible for preventing blood sugar from rising too high, there are several other hormones besides glucagon—cortisol, adrenaline, noradrenaline, and human growth hormone—that prevent it from going too low. You could say that insulin is such a powerful hormone that it needs five other hormones just to counterbalance its effects!

To see how insulin is *supposed* to work in the body, let's take a look at a metabolism that hasn't been "screwed up" yet by years of bad diet and sedentary living. Let's look at the metabolism of a mythical five-year-old child who's been living on an organic ranch, eating nothing but whole foods, breathing clean air, and getting a vigorous amount of exercise on a daily basis. (We know, we know—we haven't seen too many of these kids, either, but let's just postulate one for the sake of our discussion.)

The kid comes home from school and eats an apple. His blood sugar goes up slightly, as it always does when you eat food. The pancreas responds to this slight elevation in blood sugar by secreting a little shot of insulin, and insulin promptly goes to work rounding up the excess sugar in the kid's bloodstream and escorting it over to the muscle cells. Which is just dandy, because this boy is now going to go out and play, or ride a bike, or work on the ranch, or do some other physical activity for which those muscle cells of his require fuel.

So far, so good.

The muscle cells welcome the extra sugar, which they use for fuel, and eventually blood sugar drops back down to normal and even goes down a bit further because the muscles are eating it right up. Now the boy gets hungry again, comes home, and eats supper. All is right with the world.

However, this ideal metabolism is not *your* metabolism.

Your metabolism looks like this: You wake up late, stress hormones coursing through your body. (These stress hormones are an important factor in heart disease, and we'll discuss them at greater length later.) One of the things stress hormones do is send a primitive signal to the brain that it's time to fuel up for an emergency. So you run out the door and stop at Starbucks for a sweetened latte and a "low-fat" bran muffin that contains a gazillion calories. Your blood sugar takes off like the *Challenger*. The pancreas says, "Uh-oh, better send in the big guns this time, the guy's gone mad, there's sugar all over the place!" And it produces a bucketful of insulin to try to start bailing all that sugar out of your bloodstream and get it to the muscle cells pronto!

Except the muscle cells aren't having it.

"What do we need all this sugar for?" they ask. "This guy's just going to sit around all day pushing a computer mouse, and when he goes home, he's going to sit on the couch and play with the clicker."

So the muscle cells begin to *resist* the effects of insulin. "We're good," they say, "go somewhere else." Insulin now has no choice but to take its sugar pay-load to another location, and guess where it winds up?

Your fat cells, which happily welcome it in.

At first.

For a while, your pancreas can manage to keep up with the added demand for more and more insulin, and your muscle cells may still absorb enough sugar to keep you from becoming officially diabetic. But those elevated levels of insulin produced by excess sugar (in the diet and in the bloodstream) are not without serious consequences, including ones that directly affect the heart.

For a stunning example of this phenomenon, all we need do is look at the effect of insulin on blood pressure.

◀ WHAT YOU NEED TO KNOW

- The number one dietary contributor to heart disease is sugar, which is a far greater danger to your heart than fat.
- Sugar contributes to inflammation in the artery walls.
- Sugar is the missing link among diabetes, obesity, and heart disease.
- High sugar intakes drive up the hormone insulin, which raises blood pressure *and* increases cholesterol.
- Sugar and processed carbs raise triglycerides, which are an important and independent risk factor for heart disease.
- When sugar in the bloodstream sticks to proteins, it creates damaging and toxic molecules called *advanced glycation end products*, or AGEs.
- This same process also damages LDL, contributing to inflammation and ultimately to heart disease.

INSULIN RESISTANCE AND HIGH BLOOD PRESSURE

High levels of insulin will increase your blood pressure in a couple of ways. For one thing, insulin can narrow the artery walls. Narrower walls translate into higher blood pressure because a harder pumping action is required to get the blood through the narrower passageways.

But there's an even more insidious way in which insulin raises blood pressure.

It talks to the kidneys.

Insulin's message to the kidneys is this: *Hold on to salt*. Insulin makes the kidneys do this even if the kidneys would much prefer not to. Because the body controls sodium within a tight range, as it does sugar, the kidneys figure, "Listen, if we have to hold on to all this salt, we'd better bring on more water to dilute it so that it stays in the safe range." And that's exactly what they do. Increased sodium retention results in increased water retention. More water means more blood volume, and more blood volume means higher blood pressure. Fully 70 percent of people with hypertension (high blood pressure) have insulin resistance.¹

And this is not just theoretical. Research from Wake Forest Baptist Medical Center² demonstrates that insulin resistance is *directly* related to high blood pressure. "We found you can predict who's at higher risk for developing high blood pressure based on their insulin resistance," said lead researcher David Goff Jr., Ph.D., M.D. "The one-third of participants [in our study] with the highest levels of insulin resistance had rates of hypertension that were 35 percent higher than the one-third with the least resistance. These findings point out that reducing the body's resistance to insulin may help prevent hypertension and cardiovascular disease."³

Back to our story.

After a while, under the constant assault of more and more sugar and more and more insulin—all produced, mind you, by a sugar-heavy, high-carb diet—the fat cells start to say, "Enough, already!" They become somewhat resistant to the effects of insulin (a condition known, not surprisingly, as *insulin resistance*). Now your blood sugar is high (as it's got

nowhere left to go!), your insulin is high, and you're on the way to full-blown diabetes.

A side note to those of you who are concerned about weight: Not only does insulin load up your cells with sugar, making you fatter, it also locks the doors to the fat cells, making it fiendishly difficult to lose weight. And one reason being overweight significantly increases the risk of heart disease is that all those fat cells are loaded with chemicals that contribute mightily to inflammation!

THE INSULIN–CHOLESTEROL CONNECTION

Interesting factoid: Insulin has a profound effect on cholesterol as well. It turns up the cholesterol-making machinery by turbocharging the activity of the enzyme that actually controls the cholesterol-manufacturing machinery in your body. This enzyme—with the unwieldy name of HMG-CoA reductase—is the very same enzyme that's shut down by cholesterol-lowering drugs! You could probably lower your cholesterol—if you still care about that—by simply lowering your insulin levels. And doing so would have none of the side effects of cholesterol-lowering medication, unless you call a longer life span and better health side effects!

By the way, we're not kidding about the “longer life span and better health” part. A 1992 study examined the blood work of healthy centenarians in an effort to find out whether there were any commonalities among the members of this unusually long-lived demographic. It found three: low triglycerides, high HDL cholesterol, and—wait for it—low fasting insulin.⁴ Your diet affects two of these blood measures—triglycerides and fasting insulin—and both measures will fall like a rock when you reduce or eliminate sugar and processed carbs in your diet. Lowering triglycerides is one of the major health benefits of a diet lower in sugar, as high triglycerides are far more of a danger sign for heart disease than high cholesterol is.

Beginning to connect the dots?

“Normally, insulin has some fairly positive effects on the body, such as being anti-inflammatory,” says Jeff Volek, Ph.D., R.D., one of the top researchers in the field of diet and health.⁵ “But if you’re insulin resistant, chronically high insulin levels have the opposite effect. They actually promote inflammation and cardiovascular problems. That’s not generally appreciated yet; what is well accepted is that high glucose (blood sugar) will cause problems over time.”⁶

So insulin is *anti*-inflammatory in people with normal insulin sensitivity, but it is *highly* inflammatory in those with insulin resistance. Having insulin resistance is a double whammy when it comes to developing heart disease. Insulin resistance makes it more likely you’ll have hypertension and puts you at significantly greater risk for diabetes and obesity—all major risk factors for cardiovascular disease. But to add insult to injury, that excess insulin has an inflammatory effect on your system as well. As we’ve seen, inflammation is a major player in the development of plaque, and a far more important risk factor for heart disease than cholesterol is.

The collection of diseases strongly influenced by insulin resistance has been given the acronym CHAOS: coronary disease, hypertension, adult onset diabetes, obesity, and stroke. They’re all related, and what they have in common is insulin resistance. If you have any degree of insulin resistance, controlling your insulin by dietary means may be one of the most effective strategies for reducing the risk of coronary disease. It certainly beats the fairly irrelevant strategy of lowering cholesterol!

“[H]aving chronically elevated insulin levels has harmful effects of its own—heart disease for one,” Gary Taubes wrote in the *New York Times*.⁷ Elevated insulin increases triglycerides, raises blood pressure, and lowers HDL cholesterol—all making insulin resistance even worse and substantially upping the risk for heart disease.

At this point you may be wondering, “How do I know if I have insulin resistance?” Good question. Though there are blood measures to determine this, there’s also a nice, simple, low-tech way to do it. Stand in front of a wall and walk toward it. If your belly touches the wall before the rest of your body, there’s an excellent chance that you’re insulin resistant. Men with waist sizes of 40 inches or more are almost certainly insulin resistant, as are women with waist sizes of 35 inches or more. (Although there are,

indeed, people with insulin resistance who are rail thin, the vast majority of people with insulin resistance are not.)

Not only does insulin load up your cells with sugar, making you fatter, it also locks the doors to the fat cells, making it fiendishly difficult to lose weight.

Stand in front of a wall and walk toward it. If your belly touches the wall before the rest of your body, there's an excellent chance that you're insulin resistant.

Insulin resistance *is* reversible. And it's hardly a rare phenomenon. The prevalence of insulin resistance has skyrocketed 61 percent in the past decade alone, according to Daniel Einhorn, M.D., cochair of the AACE Insulin Resistance Syndrome Task Force and medical director of the Scripps Whittier Diabetes Institute in California.⁸ The prevalence of insulin resistance has probably been underestimated from the beginning. Gerald Reaven of Stanford University did the original work on insulin resistance in the 1980s. Here's how he approximated the number of people who were insulin resistant. He divided his test population—nondiabetic, healthy adults—into quartiles and tested their ability to metabolize sugar and carbohydrates. He found that while the top 25 percent of the population could handle sugar just fine, the bottom 25 percent could not—they had insulin resistance (or, in the parlance of researchers, impaired glucose metabolism). So for a long time, it was thought that the number of people with insulin resistance was one in four (25 percent).

But there's a problem.

What happened to the 50 percent of people *between* those two extremes? It turns out they had neither the terrific glucose metabolism of the top 25 percent nor the full-blown insulin resistance of the bottom 25 percent; instead, they fell somewhere in between. One could easily argue that because only 25 percent of the population had flawless glucose metabolism, the rest of us—up to 75 percent of the population—had *some* degree of insulin resistance! Also, Reaven used young, healthy adults as subjects, and their numbers were definitely not representative of the population as a whole—the fact is, sensitivity to insulin actually *decreases* (and insulin resistance *increases*) as you get older. The take-home point: Insulin resistance isn't just something that happens to other people. The American Association of Clinical Endocrinologists has estimated that one in three Americans is insulin resistant,⁹ and we suspect that the number is a bit higher.

Back in [chapter 3](#) we mentioned that calculating your ratio of triglycerides to HDL cholesterol is a much better way to predict heart disease than by assessing cholesterol levels. (Just so you don't have to go back and look it up, you calculate your ratio by simply looking at two line items on your blood test—triglycerides and HDL cholesterol. If, for example, your triglycerides are 150 mg/dL and your HDL cholesterol is 30 mg/dL, your ratio is 150:30, or five.) As it turns out, this same ratio is an excellent predictor of insulin resistance. In one study, a ratio of three or greater was a reliable predictor of insulin resistance.¹⁰

That same triglyceride-to-HDL ratio gives us other important information as well. As noted previously, only the small, dense, BB gun pellet-type LDL molecules are the ones that cause damage (the “bad” bad cholesterol). There are several blood tests your doctor can order that will tell you just how much of your LDL cholesterol is “bad” bad cholesterol (the BB gun pellets) and how much of your LDL cholesterol is “good” bad cholesterol (the cotton ball molecules). (Tests for particle size include the widely used NMR test; the Lipoprotein Particle Profile test, or LPP; the Berkeley cholesterol test from Berkeley HeartLab; and the Vertical Auto Profile test, or VAP.)

But the triglyceride-to-HDL ratio is also a great indicator of the kind of LDL you're packing. Those with high ratios have more of the BB gun pellet-type LDL (which is atherogenic), while those with low ratios have

more of the cotton ball molecules (harmless). Triglyceride levels higher than 120 mg/dL and HDL levels below normal (less than 40 mg/dL in men and less than 50 mg/dL in women) are usually associated with the small, dense, atherogenic LDL particles you don't want!¹¹

In fact, if you prefer not to do any math, one single number on your blood test will tell you whether your LDL cholesterol is primarily the big, fluffy, harmless kind (pattern A) or the mean, angry, small, dense kind (pattern B). Just look at your triglyceride levels.

High triglycerides in general correlate strongly with high levels of those dangerous LDL-B particles. *Low* levels of triglycerides correlate with *higher* levels of the harmless LDL-A particles. In other words, the higher your triglycerides, the greater the chance that your LDL cholesterol is made up of the kind of particles that are way more likely to lead to heart disease. And the higher your triglycerides, the greater the chance that you're insulin resistant, which in turn means that insulin is contributing mightily to the very inflammation that damages LDL cholesterol in the first place and starts the whole cycle of plaque formation. The take-home point: Reduce your triglycerides (and raise your HDL), and you reduce your risk of heart disease.

Lowering your sugar intake probably won't affect your HDL level, but it will dramatically affect two of the other three indicators of a long and healthy life: triglycerides and fasting insulin, both of which will certainly drop when you lower the amount of sugar and processed carbs you're eating (or drinking).

SUGAR: CAUGHT AT THE SCENE OF THE CRIME

We're pretty sure that if you asked a random sampling of ordinary people what part of their diet is most dangerous to their heart, the majority of them would say "fat."

They'd be wrong.

The number one dietary contributor to heart disease is sugar.

Diets that are lower in sugar and processed carbs will reduce inflammation, blood sugar, insulin, insulin resistance, *and* triglycerides. And lowering triglycerides automatically improves that all-important ratio of triglycerides to HDL. (If your triglycerides were 150 mg/dL and your HDL was 50 mg/dL, you'd have a ratio of three, but if you brought your triglycerides down to 100 mg/dL, the ratio would automatically drop to two, or 100:50. Neat, huh?)

You may remember from [chapter 3](#) a concept called the "Four Horsemen of Aging." We've already covered two of those horsemen—oxidation and inflammation—and seen how oxidation initiates the inflammation that ultimately leads to plaque formation and heart disease. Now it's time to tie up some loose ends and introduce the third horseman of aging: sugar.

Sugar is directly responsible for one of the most damaging processes in the body, something called *glycation*. (Previously, Dr. Jonny originally named glycation as one of the Four Horsemen of Aging, but because glycation is impossible without sugar, and because sugar affects heart disease in other ways as well, in this book we're going to be talking about the heart-damaging effects of sugar in general.)

Here's how it works.

Glycation is what happens when sticky sugar molecules glom onto structures and get stuck where they don't belong, essentially gumming up the works.

You see, sugar is sticky (think cotton candy and maple syrup). Proteins, on the other hand, are smooth and slippery (think oysters, which are pure protein). The slippery nature of proteins lets them slide around easily in the cells and do their jobs effectively. But when you've got a lot of excess sugar

in your system, it keeps bumping into proteins, ultimately getting stuck onto the protein molecules. Such proteins are now said to have become *glycated*. The glycated proteins are too big and sticky to get through small blood vessels and capillaries, including the small vessels in the kidneys, eyes, and feet, which is why so many diabetics are at risk for kidney disease, vision problems, and amputations of toes, feet, and even legs. The sugar-coated proteins become toxic and make the cell machinery run less efficiently. They damage the body and exhaust the immune system. Scientists have given these sticky proteins the acronym AGEs—which stands for *advanced glycation end products*—partially because these proteins are so involved in aging the body.

What does this have to do with cholesterol and heart disease? Actually, everything. You may recall our earlier discussion about LDL cholesterol in which we pointed out that LDL cholesterol is never a problem until it becomes damaged. (Remember, damaged LDL cholesterol of the BB gun pellet variety [pattern B] gets stuck to the artery walls, ultimately triggering the immune system reaction that causes inflammation.) We discussed one primary way in which LDL cholesterol gets damaged—through oxidative stress generated by free radicals.

Can you guess the other way it gets damaged?

Glycation.

So now you have sugar at the scene of several crimes, all related to heart disease. “High blood sugar causes the lining cells of the arteries to be inflamed, changes LDL cholesterol, and causes sugar to be attached to a variety of proteins, which changes their normal function,” says Dwight Lundell, M.D., author of *The Cure for Heart Disease*. High blood sugar, as we’ve seen, also sends insulin levels skyrocketing, and in most people that will lead to insulin resistance, the central player in every condition we’ve examined that is intimately connected to heart disease: diabetes, obesity, high blood pressure, and metabolic syndrome.

Is it any surprise that we think reducing sugar is far more important than reducing fat or cholesterol?

And by the way, we’re hardly the first people to say so.

The Voice of Dissent: Introducing John Yudkin

By 1970, Ancel Keys's research had been published and was being picked up by the media; the low-or nocholesterol brigade was gearing up for an assault on the consciousness of the American public. Then in 1972, Robert Atkins published *Diet Revolution*, which became the de facto poster child for the low-carb movement two decades later. Atkins advocated an approach completely opposite to the one promoted by Keys: He said that insulin and carbohydrates, not fat and cholesterol, were the problem in the American diet.

Because his high-fat, high-protein, low-carb diet went so dramatically against the conventional wisdom of the times, Atkins was attacked mercilessly in the press and vilified by the medical mainstream, which turned him into a pariah in the medical community. But in the same year that Atkins published his book, an English doctor named John Yudkin was making waves by politely and reasonably suggesting to the medical establishment that perhaps its emperor, while indeed cholesterol-free and low-fat, was nonetheless naked as a jaybird.

A professor of nutrition at Queen Elizabeth College, University of London, Yudkin was a highly respected scientist and nutritionist who had dozens of published papers in such renowned peer-reviewed journals as *The Lancet*, the *British Medical Journal*, the *Archives of Internal Medicine*, the *American Journal of Clinical Nutrition*, and *Nature*.

Yudkin was typically portrayed by his detractors as a wild-eyed fanatic who blamed sugar as the cause of heart disease, but in fact he was nothing of the sort. In his 1972 book, *Sweet and Dangerous*, he was the embodiment of reason when he called for a reexamination of the data—which he considered highly flawed—that led to the hypothesis that fat causes heart disease.

In the 1960s, Yudkin did a series of animal experiments in which he fed sugar and starch to a variety of critters, including chickens, rabbits, pigs, and college students. Invariably he found that the levels of triglycerides in all these subjects were raised. (Remember, high triglycerides are a major risk factor for heart disease.) In Yudkin's experiments, sugar also raised insulin, linking sugar to type 2 diabetes, which, as you now know, is intimately related to heart disease as well.¹²

Yudkin was one of the many who pointed out that statistics for heart disease and fat consumption existed for many more countries than those

referred to by Keys, and that these other figures didn't fit into the "more fat, more heart disease" relationship that was evident when only the seven selected countries were considered. He pointed out that there was a better and truer relationship between *sugar consumption* and heart disease, and he said that "there is a sizable minority—of which I am one—that believes that coronary disease is *not* largely due to fat in the diet." (Three decades later, Dr. George Mann, an associate director of the Framingham Heart Study, arrived at the same conclusion and assembled a distinguished group of scientists and doctors to study the evidence that fat and cholesterol cause heart disease, a concept he later called "the greatest health scam of the century."¹³)

In the same year that Atkins published the first edition of his book, an English doctor named John Yudkin was making waves by politely and reasonably suggesting to the medical establishment that perhaps its emperor, while indeed cholesterol-free and low-fat, was nonetheless naked as a jaybird.

Around the same time, the brilliant Danish scholar Uffe Ravnskov, M.D., Ph.D., reanalyzed the original Keys data and came to an identical conclusion. His exemplary scholarship is supported by hundreds of referenced citations and studies from prestigious peer-reviewed medical journals and can be found in his book, *The Cholesterol Myths*, or on his website (www.ravnskov.nu/cholesterol.htm).

Though Yudkin did not write a low-carb diet book per se, he was one of the most influential voices of the time to put forth the position that sugar was responsible for far more health problems than fat was. His book called attention to countries in which the correlation between heart disease and sugar intake was far more striking than the correlation between heart disease and *fat*. And he pointed to a number of studies—most dramatically

of the Masai in Kenya and Tanzania—in which people consumed copious amounts of milk and fat and yet had virtually no heart disease. Interestingly, these people also consumed almost no sugar.¹⁴

The Sweetening of America

To be clear, Yudkin never said that sugar *causes* the diseases of modern civilization, just that a case could easily be made that it deserved attention and study, certainly as much as, if not more than, fat consumption. Heart disease is associated with a number of indicators, including fat consumption, being overweight, cigarette smoking, a sedentary lifestyle, television viewing, and a high intake of sugar. (Yudkin himself did several interesting studies on sugar consumption and coronary heart disease. In one he found that the median sugar intake of a group of coronary patients was 147 g, twice as much as it was in two different groups of control subjects that didn't have coronary disease; these groups consumed only 67 g and 74 g, respectively.¹⁵)

“Many of the key observations cited to argue that dietary fat caused heart disease actually support the sugar theory as well,” Taubes wrote. “During the Korean War, pathologists doing autopsies on American soldiers killed in battle noticed that many had significant plaques in their arteries, even those who were still teenagers, while the Koreans killed in battle did not. The atherosclerotic plaques in the Americans were attributed to the fact that they ate high-fat diets and the Koreans ate low-fat. But the Americans were also eating high-sugar diets, while the Koreans, like the Japanese, were not.”

As Yudkin put it, “It may turn out that [many factors, including sugar] ultimately have the same effect on metabolism and so produce coronary disease by the same mechanism.” What is that mechanism? Fingers are beginning to point suspiciously to an *overload of insulin* as a common culprit at the root of at least some of these metabolic and negative health effects, such as heart disease; controlling insulin was the main purpose of the original Atkins diet and has become the *raison d'être* of the low-carb approach to living. Though the Atkins diet is certainly not the only way to control insulin, Atkins—who was after all a cardiologist—is to be commended for being prescient when it comes to identifying carbohydrates and insulin resistance as causative factors in diabetes, obesity, hypertension, and, you guessed it, heart disease.

CHOLESTEROL INSANITY

Yudkin's warnings against sugar and Atkins's early low-carb approach to weight loss were mere whispers lost in the roar of anti-fat mania. By the mid-1980s, fat had been utterly and completely demonized, and fat phobia was in full bloom, with hundreds of cholesterol-free foods being foisted on a gullible public.¹⁶ In November 1985, the National Heart, Lung, and Blood Institute launched the National Cholesterol Education Program with the stated goal of “reducing illness and death from coronary heart disease in the United States by *reducing the percent of Americans with high blood cholesterol* [italics ours].”¹⁷

In 1976, Nathan Pritikin opened his Pritikin Longevity Center in Santa Barbara, California, and for the next decade preached the super-low-fat dogma to all who would listen, which included most of the country. Pritikin died in 1985, but his mantle was quickly taken up by Dr. Dean Ornish. Ornish's reputation—and much of the public's faith in the low-fat diet approach—was fueled by his famous five-year intervention study, the Lifestyle Heart Trial, which demonstrated that intensive lifestyle changes may lead to regression of coronary heart disease. Ornish took forty-eight middle-aged white men with moderate to severe coronary heart disease and assigned them to two groups. One group received “usual care,” and the other group received a special, intensive, five-part lifestyle intervention consisting of (1) aerobic exercise, (2) stress-management training, (3) smoking cessation, (4) group psychological support, and (5) a strict vegetarian, high-fiber diet with 10 percent of the calories coming from fat.

When Ornish's study showed some reversal of atherosclerosis and fewer cardiac events in the twenty men who completed the five-year study, the public perception—reinforced by Ornish himself—was that the results largely stemmed from the low-fat diet. This conclusion is an incredible leap that is in no way supported by his research. The fact is that *there's no way to know* whether the results were because of the low-fat diet portion of the experiment (highly unlikely in our view), the high fiber, the whole foods, the lack of sugar, or some combination of the interventions. It is entirely possible that Ornish would have gotten the same or better results with a

program of exercise, stress management, smoking cessation, and group therapy plus a whole foods diet high in protein and fiber and low in sugar.

Yet low-fat eating managed to remain the dietary prescription of every major mainstream health organization. This recommendation was built on a foundation of two basic beliefs: that low-fat diets will reduce cholesterol, and that reducing cholesterol will actually reduce heart disease and extend life.

Although some studies have shown that low-fat diets do reduce overall cholesterol, many have shown nothing of the sort. When you replace fat in the diet with carbohydrates, which is exactly what low-fat diets do, you wind up with *higher* triglycerides and *lower* HDL cholesterol.

Bad news indeed. Higher triglycerides are an independent risk factor for heart disease—and raising them while lowering HDL cholesterol at the same time is a double whammy, a really bad “side effect” of the supposedly heart-healthy low-fat diet. Not only do you raise one important independent risk factor for heart disease (triglycerides) while at the same time lowering one *protective* measure (HDL cholesterol), but you *also* change the all-important ratio of triglycerides to HDL cholesterol in the worst way possible. A higher triglycerides number and a lower HDL cholesterol number mean a much *higher* ratio of triglycerides to HDL. As we’ve seen, you want your ratio to be *low*, not high; low-fat, high-carbohydrate diets make the ratio *higher*.

The Sugar Lobby in Action

So how did fat get demonized while sugar got a “get out of jail free” card?

Well, there’s no political lobby for “fat,” but there’s a powerful one for sugar.

In 2003, the World Health Organization (WHO)—not exactly a bunch of wide-eyed radicals—published a conservative, reasonable report called *Diet, Nutrition and the Prevention of Chronic Diseases*.¹⁸ In it, the WHO made the unexceptional statement that it would be a good idea for people to derive no more than 10 percent of their daily calories from added sugars. The report suggested that people could lower their risk of obesity, diabetes, and heart disease simply by curbing some of the sugar they were consuming. A completely mainstream, noncontroversial, “vanilla”

recommendation if ever there was one. Who could possibly object, you might think?

◀ WHAT YOU NEED TO KNOW

- Hypertension, high levels of triglycerides, and a high ratio of triglycerides to HDL are all better predictors of heart disease than cholesterol. Sugar, or more specifically fructose, raises every single one of these measures.
- Fat raises LDL cholesterol, but it raises the big, fluffy, harmless particles (producing the desirable pattern A profile) and lowers the nasty little BB gun–pellet LDLs that actually do cause heart disease. Sugar, in contrast, has the opposite effect, increasing the number of really bad LDL molecules (producing the harmful pattern B profile) and decreasing the number of harmless ones. On top of that, high levels of sugar and insulin damage those nasty little LDL particles, making them far more likely to start the process of inflammation.
- If you accept our theory that inflammation, not cholesterol, is at the “heart” of heart disease, it’s worth pointing out that the metabolic effects of sugar are highly inflammatory to your artery walls.

Well, the U.S. sugar industry, for one.

“Hoping to block the report . . . the Sugar Association threatened to lobby Congress to cut off the \$406 million the United States gives annually to the WHO,” reported Juliet Eilperin in the *Washington Post*.¹⁹ The *Post* quoted an April 14, 2003, letter from the Sugar Association’s president, Andrew Briscoe, to the general director of WHO in which he stated, “We will exercise every avenue available to expose the dubious nature of the *Diet, Nutrition and the Prevention of Chronic Diseases* report.”

Two senators wrote a letter to then Health and Human Services Secretary Tommy G. Thompson, urging him to squelch the report. Not soon afterward, the U.S. Department of Health and Human Services submitted

comments on the report, stating that “evidence that soft drinks are associated with obesity is not compelling.”

Oh, really? Shades of the tobacco industry’s defense of cigarettes.

In a 2005 report by the Institute of Medicine, the authors acknowledged that there was a ton of evidence suggesting that sugar consumption could increase the risk of heart disease and diabetes—and that it could even raise LDL (“bad”) cholesterol. The problem was they couldn’t say that the research was definitive. “There was enough ambiguity, they concluded, that they couldn’t even set an upper limit on how much sugar constitutes too much,” Taubes wrote.

This dovetailed nicely with the last assessment of sugar by the Food and Drug Administration (FDA) back in 1986 that basically said “no conclusive evidence on sugars demonstrates a hazard to the general public when sugars are consumed at the levels that are now current.”

“This is another way of saying that the evidence by no means refuted the [charges against sugar], just that it wasn’t definitive or unambiguous,” Taubes said. It’s also worth noting that at the time, we were consuming approximately 40 pounds per year of “added sugars,” meaning sugar beyond what we might naturally obtain from fruits and vegetables. (That comes to about two hundred extra sugar calories a day, about a can and a half of Coke.)

That doesn’t sound so bad, really, and if that were all the sugar we were consuming, most nutritionists in America would be pretty happy. The problem was it wasn’t 40 pounds a year. Even back then the Department of Agriculture said we were consuming 75 pounds a year, and by the early 2000s it was up to 90 pounds. As of late 2011, we’re up to 156 pounds a year. That’s the equivalent of thirty-one 5-pound bags for every man, woman, and child in America.²⁰

What’s So Bad about a Little Sugar?

The way in which sugar damages the heart can be directly related to insulin resistance.

Ordinary table sugar, known technically as *sucrose*, is actually composed of equal parts glucose and fructose, two simple sugars that are anything but metabolically equal. Glucose can be used by any cell in the body. Fructose,

on the other hand, is metabolic poison. It's the fructose in our sweetened foods that we should fear the most.

Before you point the finger of blame exclusively at high-fructose corn syrup (HFCS), an additive that's made it into virtually every processed food on the market, consider the following:

- Regular sugar (sucrose) is 50 percent glucose and 50 percent fructose.
- High-fructose corn syrup is 55 percent fructose and 45 percent glucose, a difference that just doesn't matter very much.
- So sugar and high-fructose corn syrup are *essentially* the same thing.

Because high-fructose corn syrup has gotten so much heat in the press, some food manufacturers now proudly advertise that their products contain none of it and are instead sweetened with "natural" sugar (meaning ordinary sucrose). Meanwhile, the Corn Refiners Association has claimed that high-fructose corn syrup is being unjustly targeted and is no worse than "regular" sugar.

Sadly, the association is technically right. Fructose is the damaging part of sugar, and whether you get that fructose from regular sugar or from HFCS doesn't make a whit of difference. That doesn't absolve HFCS at all; it just means that "regular" sugar is *just as bad* as HFCS. It's the fructose in each of them that's causing the damage, and here's why.

Fructose and glucose are metabolized in the body in completely different ways. They are *not* identical. Glucose goes right into the bloodstream and then into the cells, but fructose goes right to the liver. Research has shown that fructose is seven times more likely to form the previously mentioned artery-damaging AGEs (advanced glycation end products). Fructose is metabolized by the body like fat, and it turns into fat (triglycerides) almost immediately. "When you consume fructose, you're not consuming carbs," says Robert Lustig, M.D., professor of pediatrics at the University of California, San Francisco. "You're consuming fat."

Fructose is the major cause of fat accumulation in the liver, a condition known technically as *hepatic steatosis* but which most of us know as fatty liver. And there is a direct link between fatty liver and our old friend, insulin resistance.

A top researcher in the field of insulin resistance, Varman Samuel of the Yale School of Medicine, told the *New York Times* that the correlation between fat in the liver (fatty liver) and insulin resistance is remarkably strong. “When you deposit fat in the liver, that’s when you become insulin resistant,” he said.²¹

And all together now, class: What causes fat to accumulate in the liver? Fructose.

If you want to watch a bunch of lab animals become insulin resistant, all you have to do is feed them fructose. Feed them enough fructose and, sure enough, the liver converts it to fat, which then accumulates in the liver—with insulin resistance right behind it. This can take place in as little as a week if the animals are fed enough fructose, whereas it might take a few months at the levels we humans normally consume. Studies conducted by Luc Tappy, M.D., in Switzerland revealed that feeding human subjects a daily dose of fructose equal to the amount found in eight to ten cans of soda produced insulin resistance and elevated triglycerides within a few days.²²

Fructose found in whole foods such as fruits, however, is a different story. There’s not all that much fructose in, for example, an apple, and the apple comes with a hefty dose of fiber, which slows the rate of carbohydrate absorption and reduces insulin response. But fructose extracted from fruit, concentrated into a syrup, and then inserted into practically every food we buy at the supermarket—from bread and hamburger buns to pretzels and cereals—well, that’s a whole different animal.

High-fructose corn syrup was first invented in Japan in the 1960s and made it into the American food supply around the mid-1970s. It had two advantages over regular sugar, from the point of view of food manufacturers. Number one, it was sweeter, so theoretically you could use less of it. Number two, it was much cheaper than sugar. Low-fat products could be made “palatable” by the addition of HFCS, and before long, manufacturers were adding the stuff to everything. (Doubt us? Take a field trip to your local supermarket and start reading labels. See if you can find any processed foods that don’t contain it.)

The result is that our fructose consumption has skyrocketed. Twenty-five percent of adolescents today consume 15 percent of their calories from fructose alone! As Lustig points out in a brilliant lecture, “Sugar: The Bitter Truth” (available on YouTube), the percentage of calories from fat in the

American diet has gone down at the same time that fructose consumption has skyrocketed, along with heart disease, diabetes, obesity, and hypertension. Coincidence? Lustig doesn't think so, and neither do we.

Remember our mention of metabolic syndrome? It's a collection of symptoms—high triglycerides, abdominal fat, hypertension, and insulin resistance—that seriously increases the risk for heart disease. Well, rodents consuming large amounts of fructose rapidly develop it.²³ In humans, a high-fructose diet raises triglycerides almost instantly; the rest of the symptoms associated with metabolic syndrome take a little longer to develop in humans than they do in rats, but develop they do.²⁴ Fructose also raises uric acid levels in the bloodstream. Excess uric acid is well known as the defining feature of gout, but did you know that it also predicts future obesity and high blood pressure?

Fructose and glucose behave very differently in the brain as well, as research from Johns Hopkins has suggested. Glucose decreases food intake while fructose increases it. If your appetite increases, you eat more, thus making obesity, and an increased risk for heart disease, far more likely. "Take a kid to McDonald's and give him a Coke," Lustig said. "Does he eat less? Or does he eat more?"

M. Daniel Lane, Ph.D., of the Johns Hopkins University School of Medicine stated, "We feel that [the findings on fructose and appetite] may have particular relevance to the massive increase in the use of high-fructose sweeteners (both high-fructose corn syrup and table sugar) in virtually all sweetened foods, most notably soft drinks. The per capita consumption of these sweeteners in the USA is about 145 lbs/year and is probably much higher in teenagers/youth that have a high level of consumption of soft drinks."²⁵

All told, the case against fructose consumption as a key factor in the development of heart disease seems to us to be far more cogent than the case against fat. It's also worth pointing out that every single bad thing that fructose does to increase our risk for heart disease—and it does a lot—has virtually nothing to do with elevated cholesterol.

The fact is that sugar is far more damaging to the heart than either fat or cholesterol are, but that has never stopped the diet establishment from

continuing to stick to its story that fat and cholesterol are what we ought to be worried about.

As the old journalistic maxim goes, “Never let the facts get in the way of a good story.”

Unfortunately, this story is long past its expiration date. Sticking to it in the face of all evidence continues to make many people very sick indeed

CHAPTER 5

THE TRUTH ABOUT FAT: IT'S NOT WHAT YOU THINK

YOU CAN'T TALK ABOUT CHOLESTEROL WITHOUT ALSO TALKING ABOUT FAT, which is convenient, because it's exactly what we're going to discuss in this chapter.

When you're done reading it, you may have an entirely different perspective on fat and a much more accurate notion of what the terms "good fat" and "bad fat" mean. And no, we're not just going to tell you the stuff you've heard a million times, such as "fat from fish is good" (completely true) and "saturated fat is bad" (very far from always true).

But let's not get ahead of ourselves.

According to conventional wisdom, fat and cholesterol are the twin demons of heart disease, linked together in our minds as firmly as Hell and Damnation or Bonnie and Clyde. We've been admonished to lower our cholesterol and stop eating saturated fat. These two mandates are the basis of the diet–heart hypothesis, which has guided national health policy on healthy eating for decades and basically holds that fat and cholesterol in the diet are a direct and significant cause of heart disease.

Okay, so fat and cholesterol (whether they show up in your diet or in your bloodstream) are pretty much kissing cousins.

We've discussed cholesterol in the previous chapters, so let's clear up some misconceptions about fat—what it is, what it does, what it doesn't do—and why all this matters in the first place. Once we've done that, we'll be able to look at the relationship among heart disease, fat in the diet, and cholesterol in the blood with completely new eyes.

Let's get to work!

WHAT EXACTLY IS FAT, ANYWAY?

Fat is the collective shorthand name given to any big collection of smaller units called fatty acids. You can think of “fat” and “fatty acids” as analogous to paper money and a bunch of coins. The dollar bill is the “fat” and the coins are the “fatty acids.” Just as a dollar can comprise different combinations of coins—one hundred pennies, four quarters, ten dimes, twenty nickels, and so forth—a “fat” comprises different combinations of fatty acids.

There are more fatty acids in a big fat blob of butter than there are in a spoonful of butter, just as there are more coins in \$5 than there are in \$1, but whether you’re dealing with a spoonful of butter, a tub of lard, or a tablespoon of fish oil, all fat on earth is composed of fatty acids. The only difference between the fat in olive oil and the fat in lard is that if you looked at them under a microscope, you’d see that each is made up of a different mix of fatty acids (i.e., nickels, dimes, quarters, etc.).

There are three families of fatty acids: saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids. (There’s actually a fourth class of fatty acids called trans fats, a kind of “Franken-fat,” but we’ll address that later.) In this section we’ll concentrate primarily on saturated fat, but keep a place on your dance card for two members of the polyunsaturated family called *omega-3 fatty acids* and *omega-6 fatty acids*. They’re of special importance, and we’ll be talking about them in depth later on.

Now a word of complete candor from your authors. We wrote this book for our families. We wanted the average intelligent person who didn’t have a background in science to be able to follow the basic arguments and have a clear sense of the takeaway messages. We wanted the discussions within the book to be simple enough that they could be easily grasped by nonmedical people. And, frankly, fat is complicated.

So this is the part of the book where we could easily slip into a short course on the biochemistry of fats. It’s interesting to write about, it fills a lot of pages—and it’s deadly dull for readers. Don’t worry, we’re not going to write about the chemical structure of fat, and here’s why. What makes one fatty acid “saturated” and another “unsaturated” has to do with fairly

intricate details of fat architecture and composition that, frankly, most folks couldn't care less about. (If you're really dying to know, it has to do with the number of chemical double bonds that exist in the fatty acid's molecular chain. Mono-unsaturated fats have one double bond. Polyunsaturated fats have more than one. There. Now you know.)

And as much as we enjoy talking about this stuff and would be happy to chat about it if you met us at a cocktail party, the truth is it causes many people's eyes to glaze over pretty quickly. So if you're interested in reading about double bonds, saturation, chain length, and other cool biochemical stuff, please, by all means, be our guest! That information is widely available. It's not controversial, it's not debated, and it's not really germane to our story. So, mercifully, we've decided to forgo it here and instead give you the big picture—what you really need to know about saturated, polyunsaturated, and monounsaturated fats.

SATURATED FAT 101: EVERYTHING WE LEARNED WAS WRONG!

Saturated fats are primarily found in animal foods (meat, cheese, butter, eggs) and, less often, in certain plant foods, such as coconut, coconut oil, and palm oil. They tend to be solid at room temperature (think butter) and soften when warm.

◀ WHAT YOU NEED TO KNOW

- Saturated fat has been wrongfully demonized.
- Saturated fat raises “good” (HDL) cholesterol.
- Saturated fat tends to change the pattern of your “bad” (LDL) cholesterol to the more favorable pattern A (big, fluffy particles).
- Several recent studies have shown that saturated fat is not associated with a greater risk of heart disease. One study from Harvard concluded that “greater saturated fat intake is associated with less progression of coronary atherosclerosis, whereas carbohydrate intake is associated with a greater progression.”⁷
- In the Nurses’ Health Study, refined carbohydrates were independently shown to be associated with an increased risk for coronary heart disease.
- Omega-6 fats—e.g., vegetable oils—are pro-inflammatory.
- The balance between omega-6 and omega-3 is far more important than saturated fat intake is.
- Low-fat diets work because they reduce omega-6 fats, not because they reduce saturated fat.

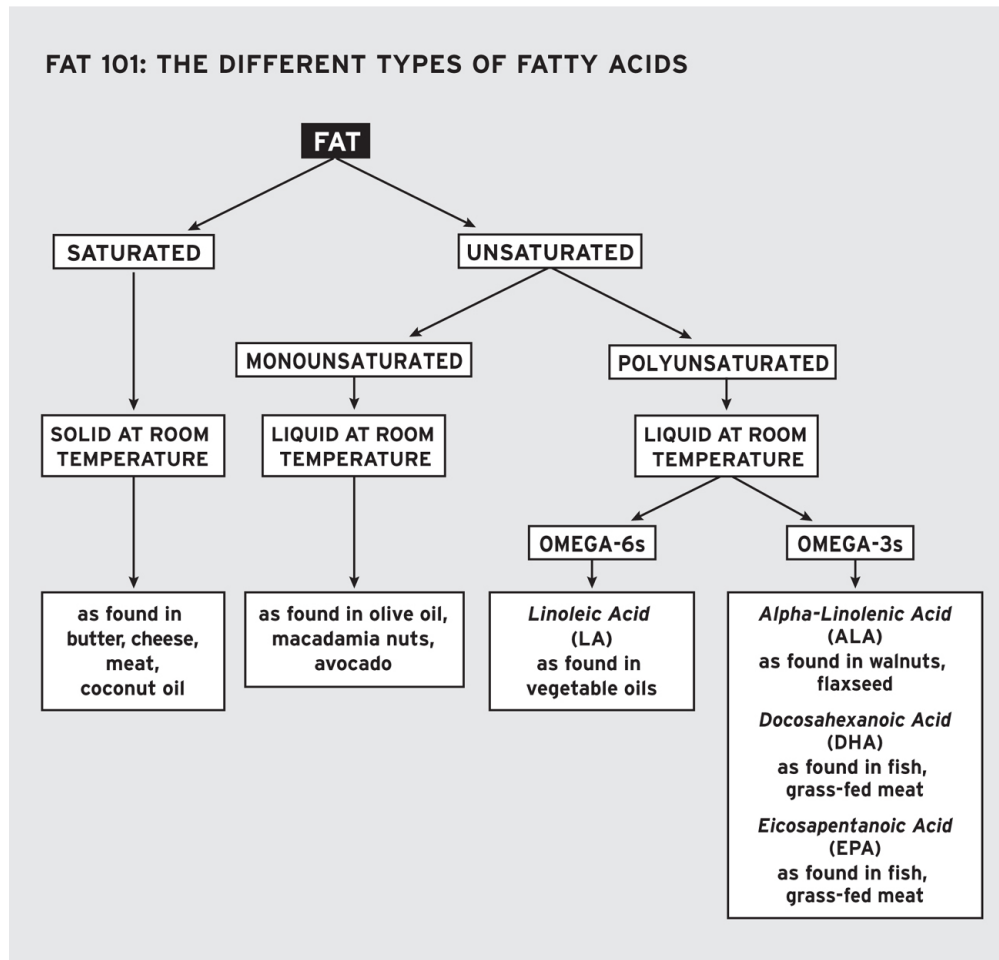


Chart by Michelle Mosher.

They also have a few other characteristics worth mentioning. Saturated fats are very stable. They're tough—when exposed to high heat they don't "mutate" or "damage" as easily as their more delicate cousins, the unsaturated fats do. That's one reason why lard (with its high concentration of saturated fatty acids) is actually a better choice for frying than the cheap, processed vegetable oils that gradually replaced it as restaurants tried to be more health conscious.

The problem with vegetable oils is that they're nowhere near as resistant to damage as saturated fats are. When you heat and reheat them for frying, as virtually every restaurant in America does, it causes the formation of all sorts of noxious compounds, including carcinogens. Compared to saturated fat, the unsaturated fatty acids in vegetable oils are much more easily damaged by high heat and more susceptible to oxidation and the production of free radicals. Those vegetable oils transform into all sorts of mutant

molecules under the stress of high heat and reheating, but when high heat is applied to saturated fat, it behaves like the strong, silent uncle at the family gathering; everyone else is going nuts, but he's calm and serene! (We'll talk about some of the other problems with the overuse of vegetable oils in our diet later on.)

Now let us ask you a question, and please answer honestly: Did you just shudder in horror when we implied a few sentences ago that using lard for cooking might actually be a good idea? You probably thought to yourself, "Now they've gone too far. Did they really say lard is better to fry with than canola oil? That's nuts!"

We'd be surprised if you didn't recoil in horror. Most people would do just that—and it's because most people have totally bought into the idea that saturated fat is the worst thing on the planet.

The idea that lard—with its high content of saturated fat—could ever be a better choice than those high-omega-6 vegetable oils that are continually pushed on us is in direct opposition to fat theology, the deeply held belief that saturated fat and cholesterol are the root of all heart disease evil. That notion has been the prevailing dogma about saturated fat, cholesterol, and heart disease for decades. By now you're more than familiar with this notion, known as the diet-heart hypothesis—it's the mantra that has guided public policy on diet and heart disease for virtually every major governmental and mainstream health organization, such as the American Heart Association.

There's only one problem.

It isn't true.

Despite its horrible reputation, saturated fat is far from a dietary demon. More and more health professionals, researchers, scientists, doctors, and nutritionists are beginning to reexamine the case against saturated fat, and they're finding that it's based on very little solid evidence (and a lot of guilt by association).

Saturated Fat and Heart Disease: Where's the Evidence?

Look, there is no shortage of studies pointing to an association between increased saturated fat intake and cardiovascular risk, but there are a few things to know about those studies.

Dr. Jonny:

When I was in fifth grade back in Queens, New York, there was a kid named A.J. who was always, and I mean *always*, getting in trouble. But it was for the most minor stuff: coming in a couple of minutes late from recess, whispering in class, or, worst case scenario, throwing a spitball. There could be five other kids doing the same thing, but A.J. would always be the one to get caught. Singled out, reprimanded, parents called in to school, the whole humiliating deal.

But there were a couple of other kids in the class who were real pieces of work. One kid, Gilbert, compulsively lit firecrackers, scaring everyone to death, and then disappeared before he could be caught at the scene of the crime. Another kid named Howie took delight in breaking people's windows with rocks. A third one, Corky, was a bully. And yet none of them ever managed to get caught. Rarely did any of these kids even get a stern talking-to. The role of the "bad kid" in the class was played by A.J., who would have to serve detention, sit in the corner, and be yelled at in front of the class, all for fairly meaningless infractions, while the kids who were doing all the really bad stuff got off scot-free.

Now it's not that old A.J. didn't do anything wrong. But unlike the other kids, he never beat anyone up, he never did anything mean, he never destroyed anyone's property—and yet whenever there was trouble, he was always the scapegoat.

I think saturated fat is like that kid A.J. It's not that it's perfect. It's just that it's far less important than the stuff we ignore—such as high intakes of omega-6 fatty acids, low intakes of omega-3s, and obscene intakes of sugar and processed carbs.

Is saturated fat so wonderful that we should all resolve to melt a ton of butter and add it to our smoothies right this minute? No, of course not. Saturated fat has some negatives. It is mildly inflammatory. It may contribute to insulin resistance.

If the dietary dictocrats are going to warn us against inflammatory food components, why choose saturated fat, a relatively minor factor in inflammation compared to the omega-6 to omega-3 ratio? If they're going to warn us about saturated fat because of its purported connection to insulin resistance, why do they continue to promote ridiculously high carbohydrate intakes, which are demonstrably worse?

Saturated fat is a lot like A.J. Not perfect, but it doesn't deserve to get beat up. And the irony is that while everyone's pushing him around and blaming him for everything bad that happens, the real culprits are getting away.

A WORD ABOUT META-ANALYSES AND WHY THEY'RE IMPORTANT

A little backstory about meta-analyses and why people do them. Say you want to learn about the sex habits of college students. There are probably a couple dozen relevant studies you could look at, but as with any other area of research, there's no guarantee that all the studies will reach the same conclusions. In fact, it's almost certain that they won't. One study might find, for example, that college kids are having more sex, while another study might find that they're actually having less. (A critical look at these two studies might uncover the fact that researchers in the two studies used slightly different definitions of the term "sex" when they surveyed the students, something that might account for the difference in results.)

Sometimes researchers overlook an obvious variable that could skew the results. Although researchers always try to control for these variables (such as age, sex, and smoking) and generally "match" subjects by the most important criteria, they don't—they can't—always control for every variable that might make a difference (and this is particularly true in diet research). The point is, if you look at anything worth studying you're going to find a whole bunch of research on it, and among those research studies you're almost guaranteed to encounter conflicting findings and areas of disagreement about how to interpret those findings.

Even something that now seems as clearly connected as the link between smoking and cancer started out as a hypothesis and had to be tested in all sorts of populations under all sorts of conditions. Studies can and do reach different conclusions depending on the statistical measures used, the populations studied, and even the definition of terms. (Is a "smoker" defined as anyone who has even one cigarette a week? Or is a "smoker" defined as someone who smokes at least half a pack a day?)

Which brings us, finally, back to meta-analysis.

Sometimes researchers gather up a whole bunch of these individual studies whose results are clustered all over the place like pins on CNN's

election maps. Then they'll ask, "What do these studies, taken together as a whole, really tell us about what's going on?" They'll gather up all the studies on, say, smoking and cancer, college students and sex, or saturated fat and heart disease. They'll examine them scrupulously, tossing out any studies whose methods, designs, or data don't meet the highest standards of research excellence. (Meta-analyses typically exclude small pilot studies, unblinded studies, studies with too few participants, or studies that do not collect data on something the researchers consider important.)

Once the "best-of-the-best" studies are selected for inclusion (and lesser studies are eliminated), the researchers go to work and apply every statistical manipulation you can imagine to tease out the real relationships from the mass of accumulated data. They look at the findings of the individual studies and compare them. They pool the subjects from all the studies. They look for trends, directions, statistical significance, and hidden relationships. And though meta-analyses themselves are not infallible, they're a great way to look at the big picture to gauge what's really going on.

Number one, the associations are far weaker than one might suspect, given how entrenched the belief is that saturated fat clogs your arteries. In many of these studies, the major "risk" examined was cholesterol, so we wind up with a circular argument in which higher saturated fat intake increases the risk for heart disease, but *only* if you accept the use of cholesterol levels as a stand-in for heart disease. Studies that measure the effect of saturated fat on heart disease and mortality *directly*—rather than indirectly by measuring its effect on cholesterol—are few and far between. But there are some important ones, which we'll discuss in a moment.

Number two, as scientists have looked more carefully at the association between saturated fat in the diet and levels of cholesterol in the blood, they are beginning to see that even here the relationship is murky. Saturated fat, as we've pointed out, does in fact raise overall cholesterol levels, but its effect is still more positive than negative, because it causes HDL levels to go up more than LDL levels. Even more important, saturated fat has a positive effect on the particle sizes of both LDL and HDL, making *more* of

the big, fluffy, benevolent particles and much *less* of the small, dense, inflammatory particles (such as LDL pattern B and HDL-3). (It's called *shifting the distribution* of LDL particles.) And, as we've been saying, the particle size of cholesterol molecules is far more important than their sheer numbers. Later, when we examine the twin principles of fat theology, you'll learn exactly why this is so and exactly why *particle size* is what we should be looking at.

One of the basic tenants of fat theology is that saturated fat increases the risk of heart disease. In the scientific literature, this issue is as far from being settled as you might think from listening to CNN. Recently, Patty Siri-Tarino, Ph.D., and Ronald Krauss, M.D., of the Children's Hospital Oakland Research Institute together with Frank B. Hu, M.D., Ph.D., of Harvard, decided to do a meta-analysis—a study of studies. In this case, they looked at all previously published studies whose purpose was to investigate the relationship of saturated fat to coronary heart disease (CHD), stroke, or cardiovascular disease (CVD). Note that this is one of those hard-to-find studies we mentioned earlier: a study of the *direct effect* of saturated fat on health. The researchers weren't just interested in the effect saturated fat had on *cholesterol*—they wanted to know the effect saturated fat had on *heart disease*. (Remember, they are *not* the same thing!)

Twenty-one studies qualified for inclusion in their meta-analysis, meaning these studies met the criteria for being well designed and reliable. All in all, the twenty-one studies included 347,747 subjects who were followed for between five and twenty-three years. Over this period of time, 11,006 of the subjects developed coronary heart disease (CHD) or stroke.

Ready for the findings?

How much saturated fat people ate predicted absolutely nothing about their risk for cardiovascular disease. In the researchers' own words, "Intake of saturated fat was not associated with an increased risk of coronary heart disease (CHD) or stroke, nor was it associated with an increased risk of cardiovascular disease (CVD)." Those folks consuming the highest amount of saturated fat were statistically identical to those consuming the least amount when it came to the probability of CHD, stroke, or CVD. Even when the researchers factored in age, sex, and study quality, it didn't change the results. Saturated fat did bupkis—it didn't increase or decrease risk in any meaningful way. Period.

“There is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD,” the researchers concluded.¹

Now—and this is a very important point—it’s not that there’s no evidence that saturated fat doesn’t raise cholesterol. There is, and we’ll examine that more in a moment. But the above meta-analysis didn’t just look at cholesterol levels; it looked at what we really care about—heart disease and dying. So never mind whether saturated fat raises my cholesterol level. What I really want to know is, what does eating saturated fat do to my chances of getting a heart attack? The meta-analysis looked at exactly that real-life endpoint we truly care about, and on that all-important metric, it found that saturated fat in the diet has virtually no effect.

That meta-analysis is hardly the only study that has found saturated fat innocent of any direct involvement in cardiovascular disease. In the fall of 2011, a new study came out in the *Netherlands Journal of Medicine* titled “Saturated Fat, Carbohydrates, and Cardiovascular Disease.” Like the above-discussed meta-analysis, its purpose was to examine the current scientific data on the effects of saturated fat, looking at all the controversies as well as the potential mechanisms for the role of saturated fat in cardiovascular disease.

Here’s what the researchers wrote:

“The dietary intake of saturated fatty acids is associated with a modest increase in serum total cholesterol, but *not* associated with cardiovascular disease [*italics ours*].”²

As we’ve been saying throughout this book, cholesterol is only used as a marker. (In other words, it’s a stand-in answer for what we *really* want to know—namely, what is the likelihood of developing heart disease?) But if you’re looking for a metric to predict who is and isn’t going to get heart disease, cholesterol—as we’ve seen in this book—is a lousy choice for a marker. If cholesterol really predicted heart disease (wrong belief number one), and if saturated fat really did terrible things to your cholesterol (wrong belief number two), then that might be reason to eliminate saturated fat from your diet.

But it turns out neither of those two things is true.

Let's take those two notions one by one, because they are the bedrock beliefs of fat theology.

FAT THEOLOGY: TWO MAIN TENETS DEBUNKED

Researchers in Japan examined the first of those beliefs—that cholesterol is a good predictor of heart disease—with another meta-analysis. They searched for all studies that had examined the relationship of cholesterol to mortality, excluding any done before 1995 and any that had fewer than five thousand subjects. Nine studies met the criteria, but four had incomplete data and so were excluded. The researchers then performed a meta-analysis on the remaining five studies, which together involved more than 150,000 people followed for approximately five years.

The researchers placed everyone into one of four groups depending on their cholesterol levels: less than 160 mg/dL, 160 to 199 mg/dL, 200 to 239 mg/dL, and higher than 240 mg/dL. (These categories mirror the American Heart Association guidelines, which state that 200 mg/dL or lower is “desirable,” 200 to 239 mg/dL is “borderline high,” and higher than 240 mg/dL is bad news indeed.)

Which group do you think would have the worst possible outcomes?

According to everything we’ve heard from the cholesterol zealots, the answer is simple: Those whose cholesterol readings were the highest (240 mg/dL and over), and even those with cholesterol readings in the “borderline” category (200 to 239 mg/dL), should be expected to die at a higher rate than those with a cholesterol level of 160 to 199 mg/dL. And those in the under 160 mg/dL category should live longest of all!

That is precisely and exactly what did *not* happen.

In fact, the group with the *lowest* cholesterol levels died at the *highest* rate.

In scientific terms, the risk for dying from any cause whatsoever (called “all-cause mortality”) was highest in the group with low cholesterol. Compared with the reference group (160 to 199 mg/dL), the risk of dying from any cause whatsoever was significantly decreased in the group having “borderline high” cholesterol of 200 to 239 mg/dL and even further decreased in the group having “high” (greater than 240 mg/dL) cholesterol.

In contrast, your risk of dying from any cause was the highest of all if your cholesterol was under 160 mg/dL!³

Total cholesterol is so irrelevant as a metric that in 2007 the Japan Atherosclerosis Society stopped using it in any tables related to the diagnosis or treatment criteria in its guidelines.

So *high* cholesterol is associated with a *reduced* risk of death? Not exactly what you might expect but exactly what the study found.

Total cholesterol is so irrelevant as a metric that in 2007 the Japan Atherosclerosis Society stopped using it in any tables related to the diagnosis or treatment criteria in its guidelines.⁴ It's not that the society abandoned the cholesterol theory, mind you. It just now relies entirely on LDL levels to determine who should be classified as having "high cholesterol," reasoning that if total cholesterol is high simply because you've got a terrifically high HDL level, that shouldn't be counted as a bad thing. Many American doctors—even the most conservative ones—would probably agree that the LDL number is the important one, even if they don't fully embrace the notion that it is the *type* of LDL—not the LDL number—that matters the most.

But is the LDL level a better predictor of heart disease or mortality than the total cholesterol level?

Once again, let's go to the videotape.

Researchers in Japan set out to answer this question in something called the Isehara Study.⁵ The Isehara Study was based on data collected from annual checkups of residents in Isehara, a smallish city (population: 100,000) located in the central Kanagawa Prefecture in Japan. A database of 8,340 men (average age sixty-four) and 13,591 women (average age sixty-one) was mined for cholesterol readings, and the 21,931 people were divided into seven groups ranked from lowest to highest LDL cholesterol

levels (in mg/dL): <80, 80 to 99, 100 to 119, 120 to 139 (reference group), 140 to 159, 160 to 179, and >180.

In both men and women, overall mortality was significantly higher in the group with the lowest LDL cholesterol levels (under 80 mg/dL).

Although it's true that in this study mortality from heart disease was greater in the group with the highest LDL levels (over 180 mg/dL, which is, admittedly, pretty darn high), this was only true in men. In women the opposite was so—fewer women died of heart disease in the group with the highest LDL levels. In any case, this increase in heart disease in the high LDL group of men was apparently more than offset by the increase in deaths from other causes.

Okay, hopefully this information will get you, and your doctor, to at least question the notion that cholesterol is an important marker or predictor of heart disease. But let's say for the sake of argument that you, or your doctor, is not quite willing to throw out the cholesterol theory. Fine, no problem. After all, you, like most of us, have been indoctrinated with the idea that anything that raises your cholesterol is bad news, and that's a hard thing to let go of, especially when you've been hearing it for your entire adult life.

But before you go back to demonizing saturated fat, let's examine the second belief that constitutes the bedrock of fat theology, the idea that saturated fat does really bad things to your cholesterol.

When cholesterol was assessed in the old-fashioned way—"total," "good," and "bad"—this idea might have made sense, because a number of studies show that saturated fat does raise total cholesterol and LDL cholesterol. And if you bought into the theory that cholesterol is a big cause of heart disease, this would be a good enough reason to give up the butter. But saturated fat actually raises HDL ("good") cholesterol more than it does LDL cholesterol, leaving the ratio between total cholesterol and HDL cholesterol—a ratio that's accepted as a measure of heart disease risk by just about everyone—unchanged or even improved.

If you eat less saturated fat and your cholesterol goes down as a result, your doc may think that's a good thing and stop looking any further. But that's the point: You can't just look at your LDL number and stop there. The reduction in LDLs that you may get from cutting out saturated fat, and the reduction in LDLs that makes everyone jump for joy and celebrate your newfound "health," comes with a hefty price: a big decrease in precisely the

LDL molecules that you want more of—the “good citizen” LDLs, those big, fluffy LDL particles that, when they’re predominant, make up a pattern A cholesterol profile.⁶ When the number of big, fluffy particles goes down, the proportion of your LDL population shifts in favor of the nasty, angry, atherogenic, BB gun pellet-type particles, giving them a kind of “majority rule.” Sure, your LDL number will go down and your doctor will be happy, but meanwhile, because of the shift in makeup of your LDL population, your risk for heart disease goes *up*.

Conversely, when saturated fat intake goes up—and carbohydrate intake goes down—the opposite happens. Now you’ll see a significant shift to more of those big, fluffy, harmless LDL particles and less of those small, dense, angry LDL particles. Your LDL population has just shifted, and the big, fluffy, harmless particles are now in the majority, leaving you in a significantly better place in terms of your heart disease risk. Sure, your overall LDL level may go up a bit, but what’s actually happened is that there are now many more “good citizens” among your LDL population and far fewer “bad” ones. In other words, you’re much better off.

The Carbohydrate Swap

For decades, most health professionals have told us that we’d be doing ourselves a huge favor if we just cut out saturated fat and replaced it with carbohydrates. And that’s exactly what most people did. After all, this idea fit nicely with the prevailing ethos: Saturated fat is bad, and “complex” carbohydrates are good. If we just swap ‘em, everyone will go home happy, and all will be right with the world.

So, as our old friend Dr. Phil might say, “How’s that working for you?”

The answer is, “Not so well.”

One important study shed light on the whole “carbs for saturated fat” swap but raised a lot of eyebrows because of its unexpected results. The study, titled “Dietary Fats, Carbohydrate, and the Progression of Coronary Atherosclerosis in Post-menopausal Women,” was conducted by the distinguished researcher Dariush Mozaffarian and his associates from Harvard Medical School.⁷

As the study title suggests, Mozaffarian set out to investigate how various fats—saturated, polyunsaturated, and monounsaturated—influenced

the progression of heart disease in postmenopausal women who ate a relatively low-fat diet. Noting that standard dietary advice has always been to eat less saturated fat, the researchers wondered exactly what terrific things would happen if you replaced terrible saturated fat with other food substances. According to the standard advice, replacing saturated fat with good stuff (e.g., carbs or “good fats” such as vegetable oils) should substantially reduce your risk for heart disease.

Except that it didn't.

“Greater saturated fat intake is associated with *less* progression of coronary atherosclerosis, whereas carbohydrate intake is associated with a *greater* progression [italics ours],” the authors concluded. “Women with higher saturated fat intakes had less progression of coronary atherosclerosis.”

Greater saturated fat intake was also associated with higher HDL levels, higher HDL-2 cholesterol levels, lower triglycerides, and an improved total-cholesterol-to-HDL ratio. Saturated fat, at least in this study, was hardly the dietary demon it's been made out to be.

And if this were not a knockout punch by itself, consider what was associated with a greater progression of coronary atherosclerosis.

Are you sitting down?

Carbohydrates.

Especially the high-glycemic, processed variety of carbohydrates, which is exactly what we tend to eat when we replace saturated fat in the diet with so-called “complex” carbs such as breads, pasta, rice, and cereal.

“The findings also suggest,” wrote the researchers, “that carbohydrate intake may increase atherosclerotic progression, especially when refined carbohydrates replace saturated or monounsaturated fats.”

“Wait a minute,” you might well say. “When I take the saturated fat out of my diet and replace it with high-glycemic carbohydrates I'm actually *increasing* my risk for heart disease?”

Dr. Sinatra: The Case Against Canola Oil

Back in 1997, I wrote an article for *Connecticut Medicine* about oxidized LDL and free radicals. I was very gung ho about canola oil at the time—as were most of my colleagues—and I was emphatic in my recommendation of it.

But the paper was rejected.

A Yale professor of medicine who was on the peer review board—a biochemist, in fact—reviewed the paper and nixed it for publication. But he was kind enough to suggest some review articles on canola oil in the literature.

I read them.

My reaction: “What have I been smoking all these years?”

The success of canola oil and its reputation as the healthiest of oils is a triumph of marketing over science. It’s a terrible oil. It’s typically extracted and refined using very high heat and petroleum solvents (such as hexane). Then it undergoes a process of refining, degumming, bleaching, and—because it stinks—deodorization using even more chemicals. The only kind of canola oil that could possibly be okay is organic, cold-pressed, unrefined canola oil, and hardly anyone is using that.

Our friend Fred Pescatore, M.D., bestselling author of *The Hamptons Diet* and former medical director of the Atkins Center, is something of a cooking oil expert. Here’s what he had to say about canola oil: “I would never use this stuff!”

If you’d like to read more about the dark side of canola oil, check out the definitive paper by lipid biochemist Mary Enig and Weston A. Price Foundation president Sally Fallon. Widely available online, it’s called, tellingly, “The Great Con-Ola.”

As for my 1997 paper, I revised it, removing the recommendation to use canola oil. The paper was accepted and published.

Dr. Jonny: Good Carbs, Bad Carbs

Whenever I give a talk about healthy eating and I mention that a diet very high in carbohydrates is problematic for most people, I'm very careful to add the caveat: "I'm not talking about fruits and vegetables!" So here's a quick cheat sheet on "good" versus "bad" carbs.

Good carbs include the following foods:

- Fruits
- Vegetables
- Beans and legumes

Bad carbs, which cover almost all carbs that come in a box with a bar code*, include:

- Cereals
- White rice
- Pasta
- Breads
- Cookies
- Pastries
- Snack foods
- Sodas
- Juice drinks
- Crackers

* There are exceptions in the categories of cereal and bread, but they are few and far between. Oatmeal is one example (but not the instant kind). Ezekiel 4:9 bread is another. But by and large if you stay away from most of the foods on the above list—or keep them to an absolute minimum—you'll be much better off healthwise.

Um, yes.

By the way, Mozaffarian and his research team didn't just look at cholesterol. They looked at actual clinical events, such as heart attacks and deaths, from any type of cardiovascular disease. They also looked at lesser known metrics that only your doctor will appreciate (such as coronary revascularization and unstable angina).

Bottom line: Greater saturated fat intake didn't increase the risk for any of them.

Vegetable Oils: Myths and Myth-Conceptions

The researchers also tested what happens when you replace saturated fat with polyunsaturated fat (such as vegetable oils), the conventional dietary advice given by just about every major health organization. Maybe high-sugar carbs aren't so good for us after all, but what about the much-touted vegetable oils, which contain the "healthy fat" our doctors keep telling us about? Swapping saturated fat for a nice helping of healthy vegetable fat has got to be just the ticket to heart health, right?

So the researchers looked at the effect of replacing saturated fat with polyunsaturated fat. Just for fun, they also took a look at what happens when you swap carbs for polyunsaturated fat.

When carbs were replaced with polyunsaturated fat there was no change in atherosclerotic progression—in terms of heart disease risk, it was a wash. But when saturated fat was replaced with polyunsaturated fat, there was a big change—but not in the expected direction. Replacing saturated fat with polyunsaturated fat actually led to an *increase* in the progression of coronary atherosclerosis!⁸ (This seemingly crazy finding will make a lot more sense when we discuss those special classes of polyunsaturated fat mentioned earlier in the chapter, omega-3s and omega-6s. Stay tuned.)

If you're confused by these findings, you're hardly alone. The *American Journal of Clinical Nutrition* devoted an entire editorial to the findings titled "Saturated Fat Prevents Coronary Artery Disease? An American Paradox."⁹ But it's only a paradox if we refuse to question the bedrock belief of fat theology that saturated fat consumption increases the risk for heart disease. The research is showing that it does not.

We worry deeply about the wholesale, unqualified recommendation to reduce saturated fat at all costs, because it invariably means that people will replace it with processed carbohydrates. That switcheroo is just about guaranteed to both reduce HDLs and increase triglycerides, and if you're trying to prevent heart disease, those are very bad outcomes indeed.¹⁰ In the Nurses' Health Study, for example, refined carb-ohydrates and their high glycemic load were independently shown to be associated with an increased risk for coronary heart disease.¹¹

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GLYCEMIC INDEX AND GLYCEMIC LOAD

Glycemic index is a measure of how quickly a given amount of food raises your blood sugar (and keeps it elevated). Glycemic load is a related (and more accurate) measure of the same thing. High-glycemic foods—such as most white breads, white rice, and cereals—are simply those that send your blood sugar on a roller-coaster ride. Low-glycemic foods include most fruits and vegetables as well as beans and legumes.

Now don't misunderstand us. If you wanted to swap some saturated fat out of your diet and trade it for some low-sugar, high-fiber, nutrient-rich carbohydrates, such as Brussels sprouts or kale, no one would complain. Substituting saturated fat with low-glycemic carbs such as vegetables doesn't increase the risk of heart attacks at all, but substitution of saturated fat with high-glycemic carbs does—by a fair amount, actually. A study in the *American Journal of Clinical Nutrition* found that replacing saturated

fats with high-glycemic index carbs was associated with a 33 percent increase in heart attack risk.¹² Because most people replace saturated fat with exactly these kinds of processed, high-glycemic (high-sugar) carbs (e.g., breads, cereals, and pasta), the conventional wisdom to cut out saturated fat and consume lots of carbs instead is starting to look like an increasingly boneheaded notion. Although it's not perfect, saturated fat does a number of good things in the body. Its wholesale replacement by the worst kind of carbohydrates is turning out to be a cure worse than the disease.¹³

A recent Dutch study added to the list of accumulating research showing that when you substitute high-glycemic carbohydrates for saturated fat you actually increase cardiovascular risk.¹⁴ But the Dutch researchers had an interesting take on this, one that appreciates that an accumulation of saturated fat in the body is not necessarily the best thing in the world.

They pointed out that eating a high amount of carbs causes your body to hold on to the saturated fatty acids that you're also consuming—and those saturated fats get preserved, stored in your body rather than burned for energy. Meanwhile, all those extra carbs you're eating get converted into more saturated fatty acids in the liver. Now you've got a serious excess of saturated fatty acids—you're holding on to the ones you're eating, and your liver is creating even more of them, fueled by the carbs you're consuming. Because large amounts of saturated fat can lessen the anti-inflammatory actions of HDL cholesterol,¹⁵ this isn't a good situation.

However, the Dutch researchers correctly noted that cutting saturated fat out of the diet is not the most effective way to combat the accumulation of saturated fatty acids in the body. It's far better, they suggested, to reduce dietary carbohydrates. This way, your body makes fewer saturated fatty acids, and its tendency to hold on to those you do eat is reduced. "Attention should be shifted from the harmful effects of dietary saturated fat per se to the prevention of the accumulation of saturated fatty acids (in the body)," the authors wrote. "This shift would emphasize the importance of reducing dietary carbs, especially carbs with a high glycemic index, rather than reducing dietary saturated fat."¹⁶

Carbohydrates have a nasty effect on cholesterol particle size, which, as you've seen, is of significantly greater importance than total cholesterol,

LDL, or even HDL. Two researchers from the Department of Atherosclerosis Research, part of the Children's Hospital Oakland Research Institute in California, decided to test the effect of dietary carbohydrates on the size and density of both LDL and HDL. They found that people who ate more carbohydrates—particularly simple sugars and starches with a high glycemic index—had significantly greater levels of those angry, dense, atherogenic particles of LDL (pattern B). They also had the greatest number of small, dense HDL particles.¹⁷

Fat in the Diet: Our Perspective

We want to propose a different way of looking at fat intake. We think what we are about to suggest goes a long way toward explaining the contradictory findings, or apparently contradictory findings, on saturated fat, diet, fat reduction, and cardiovascular disease.

To do this, we have to briefly introduce the other two categories of fats besides saturated: monounsaturated fats and polyunsaturated fats. (Remember, all fatty acids fall into one of these three broad categories.)*

Monounsaturated fat is the fat that's predominant in olive oil (as well as in nuts and nut oils, such as macadamia nut oil). Its health benefits have been well documented and are noncontroversial. Monounsaturated fat is the primary fat consumed in the highly touted Mediterranean diet, and it's generally accepted that this kind of fat is perfectly healthy. For that reason, we won't spend much time on it, because it is pretty irrelevant at this point to the case we're about to make.

The real action is with polyunsaturated fats.

Remember, polyunsaturated fats, which are primarily found in vegetable oils, are the very ones we've been admonished to include more of in our diets. When lard was slammed back in the early part of the twentieth century, the health dictocrats started their cheerleading effort for vegetable fats. (The first major beneficiary of this all-out campaign to make vegetable fats synonymous with "healthy" fat was actually the trans fat-laden Crisco, the most popular vegetable shortening of its time.) Even now, most people believe that substituting vegetable oil for animal fats is universally a good thing.

But is it always?

Let's, as they say, go to the videotape.

Polyunsaturated fats as a whole are divided into two subcategories: omega-3 fatty acids and omega-6 fatty acids. (For those who've always wondered what the heck an "omega" is anyway, you can think of the terms *omega-6* and *omega-3* as real estate terms; they're simply descriptions of the location of certain chemical structures—called double bonds—within the fatty acid. An omega-3 has its first double bond at the third carbon atom in the chain, while omega-6 has its first double bond at the sixth carbon atom in the chain. Now, for our purposes, you can promptly forget all that and just concentrate on what these two types of fatty acids—omega-3s and omega-6s—actually do in the body.)

Omega-6s, as mentioned, are found primarily in vegetable oils and some plant foods. Omega-3s are found primarily in fish, such as salmon, and certain animal foods, such as grass-fed beef, as well as in some plant foods, such as flax and flaxseed oil. So far, so good.

Here's where it gets tricky.

Both inflammatory and anti-inflammatory hormones, known as *eicosanoids*, are made in the body from polyunsaturated fats. (And to answer the inevitable question, yes, we actually need both. Inflammatory compounds are a necessary part of the immune system and play a big part in the healing process when you have a wound or other type of injury.)

Omega-6s are the precursors to the inflammatory compounds in our body—they're the building blocks the body uses to make these inflammatory hormones (specifically *series 2 prostaglandins*). And omega-3s have the opposite function: The body uses omega-3s as building blocks for the anti-inflammatory compounds (known as *series 1 prostaglandins* and *series 3 prostaglandins*).

A ton of research has established that the ideal ratio of omega-6s to omega-3s in the human diet is somewhere between 1:1 and 4:1. This seems to be the best balance to keep inflammation in check and everything running smoothly. It's the ratio found in the diets of both hunter-gatherers and healthy indigenous societies where heart disease is rare.¹⁸

But the ratio of omega-6s to omega-3s in Western diets is anywhere from an astonishing 15:1 to an even more astonishing 20:1 in favor of omega-6s.¹⁹ If you think of the inflammatory and anti-inflammatory hormones as

two armies that work together in the body to create balance in the body, that means we're overfunding the inflammation army by 1,500 to 2,000 percent!

The Law of Unintended Consequences

Our extraordinarily high intake of vegetable oil has another unintended consequence, and one that may have a profound effect on cardiovascular health. To understand it, though, you have to take a short excursion into the world of omega-3 fatty acids. (Trust us, it's a short and easy trip.)

You see, there are actually three omega-3 fatty acids—ALA (*alpha-linolenic acid*), EPA (*eicosapentaenoic acid*), and DHA (*docosahexaenoic acid*). The only one that is “essential” in the diet is ALA, which is found in green, leafy vegetables and in flaxseeds, chia seeds, perilla seeds, and walnuts. That doesn't mean the other two aren't important. In terms of their overall effects on human health, the other two are probably *more* important than ALA. The reason the other two—EPA and DHA—aren't considered “essential” is that scientists use the word *essential* in a different way than regular people use it in ordinary conversation. In this context, *essential* simply means that it's something the body can't make, so you have to get it from your diet. Your body can make EPA and DHA, so technically they're not classed as “essential.” Because the body can't make ALA, however, it's considered an “essential” omega-3.

But the fact that the body can make EPA and DHA from ALA doesn't mean it does a particularly good job of it. It converts the ALA from the diet into EPA and DHA using enzymes and a complicated series of operations known as *elongation* and *desaturation*, the success of which is influenced by many different factors, including the amount of inflammatory omega-6's in the diet. Even under the best of circumstances, only a small amount of ALA successfully gets converted into the very critical EPA and DHA.

Omega-6s and omega-3s compete for the same enzymes, and when omega-6 intake is very high, it wins the competition by default. A high intake of omega-6 reduces the conversion of ALA into EPA and DHA, which might be another reason why high omega-6 diets contribute to heart disease.¹⁹ So not only are those omega-6 fatty acids pro-inflammatory on their own, but they also reduce the body's ability to produce two of the most anti-inflammatory substances on the planet: the omega-3s EPA and DHA. It's a double whammy, and your heart is the loser.

No, the omega-6s that have been the darling of the high-carb, low-fat movement, the vegetable oils we've been told to use instead of animal fats—the very vegetable oils that “saturate” (no pun intended) our diet through their incorporation into virtually every baked, fried, and processed food available in the supermarket, the very vegetable oils that restaurants proudly boast of using because they're so “healthy”—are actually turning out to be as bad as, or worse than, the original saturated fats (such as lard) that they replaced, just as margarine turned out to be far worse than butter.

The vegetable oils we've been told to use instead of animal fats are actually turning out to be as bad as, or worse than, the original saturated fats (such as lard) that they replaced, just as margarine turned out to be far worse than butter.

For example, the primary omega-6 fatty acid—linoleic acid—has been shown to increase the oxidation of LDL cholesterol, thus increasing the severity of coronary atherosclerosis.²¹ One research study showed that a diet enriched with linoleic acid increased the oxidation of the small, nasty LDL particles, precisely the cholesterol particles that are most dangerous and most involved in the formation of arterial plaque.²² Omega-6s even inhibit your body's ability to fully incorporate the EPA you get from fish or fish oil supplements into the cell membranes, which is meaningful because EPA is the omega-3 that has the most profound effect on the heart.²³

Published values for omega-6 intake closely track observed coronary heart disease death rates for all sorts of populations worldwide.²⁴ And in the famous MRFIT study, subjects with the lowest ratio of omega-6 to omega-3 (i.e., those with the lowest intakes of omega-6 relative to their omega-3 intakes) had the lowest death rate.²⁵

The Paradox of the Ultra-Low-Fat Diet

At this point you may well be wondering why low-fat, high-carb diets work at all when they do work. If saturated fat is not the bad guy we thought it was, and if carbohydrates aren't always the good guys, why is it that some of these high-carb, super-low-fat programs seem to work sometimes?

Glad you asked, because we have a theory about that.

Although many people may believe that extremely low-fat diets work because they cut out saturated fat, we suspect the real benefit comes from reducing omega-6s. Omega-6 is the predominant fat we consume, and as we've seen, we consume way too much of it. When we follow a very low-fat diet we consume less of it, which automatically lowers the pro-inflammatory to anti-inflammatory ratio. The fact that saturated fat is lowered is actually incidental.

In addition, those famous low-fat, high-carb diets, such as those promoted by McDougall, Ornish, and Esselstyn, are remarkably low in sugar. The carb content may be high, but they're not the carbs most people are gorging on. The carbs in these high-carb diets tend to be vegetables, fruits, and a smattering of starches, such as beans and brown rice. And although some of the starches may be high-glycemic (such as potatoes), they don't contain a ton of fructose (as do most processed carbs and virtually all packaged goods). Fructose is the most metabolically dangerous of the sugars, and it is a very minor player in any of the low-fat, high-carb diets that are successful. We suspect that when very low-fat, high-carb diets work at all—and they frequently don't—they work because of these three dietary factors: fewer inflammatory omega-6s, fewer high-glycemic carbs, and much less fructose or sugar. We believe that whatever benefits might sometimes accrue from extremely low-fat, high-carb diets could be easily achieved by simply reducing sugar and processed carbs, eliminating trans fats, *increasing* omega-3s, and *decreasing* omega-6s. Reducing saturated fat and dietary cholesterol intakes has virtually nothing to do with it.

Besides, what is the mechanism by which saturated fat could cause heart disease? In 2008, the distinguished biochemist Bill Lands attempted to answer this and other related questions about conventional dietary advice in a closely argued review (complete with 231 scientific references) that was published in the scientific journal *Progress in Lipid Research*.

Here's what Lands had to say about saturated fat and heart disease:

“Advice to replace saturated fat with unsaturated fat stimulated my early experiments in lipid research. It made me ask by what mechanisms could saturated fats be ‘bad’ and unsaturated fats ‘good’ . . . Fifty years later, I still cannot cite a definite mechanism or mediator by which saturated fat is shown to kill people . . . The current advice to the public needs to identify logical causal mechanisms and mediators so we can focus logically on what food choices to avoid.”²⁶

When it comes to the theory that saturated fat kills people, Lands was essentially challenging his researcher colleagues to “prove it.”

And they haven’t.

CHAPTER 6

THE STATIN SCAM

STEPHANIE SENEFF ALWAYS WANTED TO BE A BIOLOGIST.

For as long as she can remember, she has been fascinated by how things work, particularly how living things work. She wanted to know how frogs jump, how grasshoppers breathe, how cells communicate, how the heart talks to the brain, all of which scientists study in detail, frequently by spending hours a day peering into a microscope. She was interested in systems, and to her the human body was the most fascinating system of all. So she was more than a little delighted when, after high school, she was accepted into the biology program at MIT.

After completing her B.S. in biophysics, she entered the MIT Ph.D. program and spent a year working under Professor Harvey Lodish in the laboratory headed by future Nobel Prize winner David Baltimore.

But there was a problem.

After a year in Baltimore's lab, Seneff realized two things. One, she wasn't really cut out for the isolation required by a life in the lab, and two, she wanted to start a family. So she quit the Ph.D. program.

But she didn't quit MIT. "In those days," she told us, "you could get a job as a programmer with no prior experience. I got a job at MIT Lincoln Laboratory, where I lucked into a group of pioneers in the fledging field of computer speech processing."

Voilà. Seneff found a home, a perfect blend of her two great interests—biology and computer dialogue systems. She went on to earn a Ph.D. in electrical engineering from MIT, ultimately publishing more than 170 papers and becoming one of the world's leading experts in blending biological systems with computer intelligence. (It was her pioneering work in the field of voice recognition and computer systems that led to

commercial applications such as SIRI, the virtual assistant built into the iPhone, which has an uncanny ability to recognize what you say to it and execute voice commands.

Then something happened: Seneff's husband was diagnosed with heart disease.

His doctor put him on a high-dose statin—four times the usual dose—and told him it was imperative that he stay on it. “If you go off this, or even reduce the dosage, I can no longer be your doctor,” his physician told him.

Almost immediately, the side effects started. He developed debilitating shoulder problems; muscle aches and weakness (he could no longer open drawers or jars); cognitive and memory problems; and depression, something he had never experienced before.

We all know what we do when we first get a diagnosis, or are prescribed a medication we're not familiar with, or begin having a bunch of unexplained symptoms or side effects: We go on the Internet, which is exactly what Seneff did.

Except Seneff, as you can probably imagine, is no ordinary Googler. She applied her not inconsiderable, methodologically precise skills as a researcher to the task at hand and proceeded to try to learn everything there was to learn about cholesterol, heart disease, and statin drugs. She had no agenda, other than to help her husband get well. She had not spent four years in medical school being subtly influenced by the drug companies, had not been a consultant to the pharmaceutical industry, had not been visited daily by a charming crew of pharmaceutical company reps spinning studies—paid for by those same pharmaceutical companies—that tout the unabashed benefits of their products. And she had not been paid hefty fees by those same pharmaceutical companies (like Dr. Sinatra had) to give “educational” lectures on behalf of their products (lectures that are little more than marketing tools disguised as scholarship).

Basically, she wasn't bought or influenced by or beholden to anyone in the heart disease–cholesterol–statin drug establishment. She had no preconceived ideas, either positive or negative, about what she'd find. Her research for the next few years was motivated primarily by two things: one, helping her husband get well, and two, her lifelong interest in biology and nutrition.

And let's remember that we're talking about someone whose ability to understand systems, theory, statistics, interpretation, experimental bias, confounding variables, and all the rest of the esoterica associated with evaluating studies is nothing short of world-class.

Here's what Seneff told us about statin drugs when we contacted her for this book: "Statin drugs are toxic. I liken them to arsenic, which will slowly poison you over time." (P.S.: Seneff's husband terminated his statin therapy, and all of his symptoms disappeared. Needless to say, he switched to a different doctor.)

THE NEXT MEDICAL TRAGEDY?

Seneff has become one of the most respected and outspoken critics of the cholesterol hypothesis, and she is quite vocal about her opposition to statin drugs, which she believes are the next medical tragedy waiting to happen.

Let's be clear: Although Seneff and other independent researchers are pretty unequivocal in their negative appraisal of statin drugs, we are a little more moderate. (Just a little.) Neither of us, especially Steve, believes that statin drugs are all bad. As mentioned earlier, Steve still prescribes them very occasionally, in certain limited circumstances (to middle-aged men who have already had a heart attack and are at very high risk for another). Even Duane Graveline, M.D., perhaps the most outspoken critic of statins on the planet and author of *Lipitor: Thief of Memory*, lists low-dose statin therapy as one possible option for "high-risk" people.

Statin drugs do some good in some circumstances, but their benefits, and the circumstances in which they are appropriate, are much more limited than the pharmaceutical companies would have us believe. Further-more, any good they may accomplish has little to do with cholesterol lowering, as you will soon see.

Statin drugs are anti-inflammatory. They lower C-reactive protein (a protein in the blood that's an excellent measure of systemic inflammation), and they decrease blood viscosity (meaning they make the blood flow more easily). Any of the benefits, however mild they are in reality and however overstated they are in promotional materials, are almost definitely related to these other two effects, not to the drugs' fairly meaningless ability to lower cholesterol.

(In fact, when you finish reading this section, you may find that you agree with a growing number of health professionals who think that statin drugs would be even *more* effective if they *didn't* lower cholesterol. But we digress.)

If you still doubt that the cholesterol-lowering effect of statins is the least important thing they do, put on your detective hat for a moment, and consider the following:

Prior to the introduction of statin drugs in the 1990s,* there were a number of studies done in which cholesterol was successfully lowered by

other drugs, notably the class of drugs known as *fibrates*, the go-to treatment for high cholesterol prior to the near-universal switch to statins in the last decade of the twentieth century. These drugs actually lowered cholesterol quite well, thank you very much. If lowering cholesterol does in fact prevent heart attacks or strokes, then we should see a significant reduction in heart attacks and strokes anytime we successfully lower it, regardless of the particular drug (or diet) used to accomplish this.

But investigations of the cholesterol-lowering studies prior to the mainstream use of statin drugs showed quite the opposite. And there's proof, all cataloged, collected, and assembled in one place, thanks to a man named Russell Smith.

“DYING WITH CORRECTED CHOLESTEROL IS NOT A SUCCESSFUL OUTCOME”

Back in the late 1980s, Russell Smith, Ph.D., an American experimental psychologist with a strong background in physiology, math, and engineering, decided to write the most comprehensive and critical review of the diet–heart disease literature yet seen. Published in two volumes that spanned more than six hundred pages and contained three thousand references, it was titled *Diet, Blood Cholesterol, and Coronary Heart Disease: A Critical Review of the Literature*.

◀ WHAT YOU NEED TO KNOW

- The benefits of statin drugs have been widely exaggerated, and any benefit of these drugs has nothing to do with their ability to lower cholesterol.
- Statin drugs deplete coenzyme Q₁₀, one of the most important nutrients for the heart. Depletion of CoQ₁₀ can cause muscle pain, weakness, and fatigue.
- The brain depends on cholesterol to function optimally. Cholesterol helps stimulate thinking and memory.
- Statin drugs lead to a reduction in sex hormones, as shown by several studies. Sexual dysfunction is a common (but underreported) side effect of statin drugs.
- Statins interfere with serotonin receptors in the brain.
- There are troubling indicators that statin drugs may be associated with a higher risk for cancer and diabetes.
- A comprehensive study by a University of California, San Diego, School of Medicine researcher showed that a majority of doctors *dismiss* complaints of side effects from statins and do *not* report them to MedWatch, the FDA's system for reporting any undesirable experiences associated with the use of medical products or drugs (experiences collectively known as "adverse events"). In other words, side effects are grossly underreported.
- Statins should not be prescribed for the elderly or for the vast majority of women, and they should *never* be prescribed for children.
- Research show that (with rare exceptions) any benefit from statin drugs is seen only in middle-aged men with documented coronary artery disease.

In the vast majority of studies reviewed, there was no difference in the number of deaths between the group that lowered its cholesterol and the group that didn't.

Then in 1991, together with Edward Pinckney, M.D., an editor of four medical journals and former coeditor of the *Journal of the American Medical Association*, Smith published a summary of this massive work in a book called *The Cholesterol Conspiracy*.

Among many other things, Smith and Pinckney reviewed all of the cholesterol-lowering trials that had been done prior to 1991. The studies found that using drugs to lower cholesterol was quite effective—at lowering cholesterol. The problem was that they weren't much good for anything else. If cholesterol lowering was in fact the holy grail of preventing heart disease and death, then we would expect the research to show a reduction in heart attacks, strokes, and deaths when cholesterol was effectively lowered, wouldn't we?

Let's see what Smith and Pinckney had to say about that:

“Drugs were used to lower blood cholesterol levels in twelve trials (i.e., studies). Eight of these trials were both randomized and blinded.* Of the eight that met this standard, total deaths in six trials were the same or greater in the treatment group than in the control group. For the remaining four trials (either nonrandomized or unblinded), there were no differences between the treatment group and the control group.”

Translated into clear English: In the vast majority of the studies reviewed, there was no difference in the number of deaths between the group that lowered its cholesterol and the group that didn't. In fact, in a few cases, more people died in the group that lowered its cholesterol.

Okay, so much for ten out of those twelve trials—pretty dismal results. But what about the remaining two trials?

In these two trials, there were fewer deaths in the group treated with cholesterol-lowering drugs than in the control group. These two studies, accounting for only a sixth of the total number of drug studies conducted,

the rest of which showed no benefit, were exactly the ones the cholesterol establishment seized on as “proof” of the link between cholesterol and heart disease. “However,” reported Smith and Pinckney, “one of these trials was conducted by a pharmaceutical company, which evaluated its own cholesterol-lowering drug.¹ The second trial involved an estrogen drug that produced more harm than good in three other trials.² Therefore, both of these trials are suspect.”

Scorecard: Out of twelve studies, ten showed no benefit; the two that did were both questionable.

Choosing one or two studies that show a positive result and burying the ones that don’t is a well-documented tactic of the pharmaceutical industry. It’s akin to finding two white checkers in a bucket of black ones and then holding up the white ones and claiming they’re proof that all checkers are white.

Back to the scorecard.

Smith and Pinckney now turned their attention to sixteen randomized and blinded studies that looked at the combined effect of drugs and diet on lowering cholesterol. “The total numbers of all-cause deaths in the treatment groups were the same as or greater, statistically speaking, than those in the control groups for fourteen of those trials,” they wrote. “The total numbers of coronary heart disease deaths in the treatment groups were the same as or greater than those in the control groups for fifteen of these trials. And the total number of nonfatal coronary heart disease events in the treatment groups were the same as those in the control groups for fifteen trials.”

Did your eyes just glaze over? No problem. Allow us to translate. If you define “benefit” as a lower amount of fatal or non-fatal heart attacks, a whopping fifteen out of sixteen studies showed exactly zero benefits from lowering cholesterol. Whoops.

The authors of this exhaustive review of the literature summed up their findings thusly:

“In effect, the clinical trial data overwhelmingly demonstrated no benefits of cholesterol-lowering for either coronary heart disease deaths, nonfatal coronary heart disease events, or all-cause deaths.”

So prior to the introduction of statin drugs, it was overwhelmingly clear that lowering cholesterol by itself did virtually nothing to prevent a single death or even to affect coronary heart disease in any meaningful way. Therefore, if any positive effects were to be seen in the studies using the new statin drugs (as opposed to the old cholesterol-lowering drugs), these beneficial effects couldn't possibly be due to lowered cholesterol.

As Smith and Pinckney conclusively demonstrate, all thirty or so studies completed prior to 1990 showed that you could lower cholesterol to your heart's content without adding a single day to your life. John Abramson, M.D., a professor of medicine at Harvard Medical School and the author of *Overdosed America*, recently summed up the problem perfectly in the medical journal *The Lancet*: "You can lower cholesterol with a drug, yet provide no health benefits whatsoever. And dying with corrected cholesterol is not a successful outcome."

Statin Drugs: Risks versus Benefits

Let's review: Lowering cholesterol, as the thirty-some odd studies prior to 1990 showed, accomplishes nothing (except, of course, lowering cholesterol). If there's a benefit to statin drugs at all, that benefit has to be coming from something *other* than their ability to lower cholesterol.

Now, one might reasonably argue, *so what?* Suppose you're right that the ability of statin drugs to lower cholesterol is irrelevant, but suppose they do a lot of good anyway? Why not just use them for their other benefits?

Good question. But to answer it, we need to know two things: One, just how great a benefit do we actually *see* with statin drugs? And two, what are the side effects?

In simple terms, we'd want to know: What are we risking, and what are we getting?

Only when we know the answers to these two questions can we make a smart decision about whether to go on a statin drug (or any drug, for that matter). We want to know what the risks are so we can calculate whether those risks are worth taking, which means we have to know exactly what we're likely to gain. For example, if your risk in taking a drug was a one in one hundred chance of getting a mild tummy ache, but the potential benefit was lowering your risk of cancer by 25 percent, you would probably take

that drug in a heartbeat. Why? Because the potential benefit is so great and the potential downside is so small. On the other hand, if the risk of taking a drug was a 40 percent chance of hair loss, and the potential benefit was shortening the length of a cold by a few hours, you might decide that the benefit is way too insignificant to justify even the possibility of going bald!

With that in mind, let's take a look at the side of statin drugs you probably don't know about. (No surprise here—this is not exactly the data that manufacturers of these drugs are dying to publicize.)

THE DARK SIDE OF STATIN DRUGS

Besides being far less effective than you've been led to believe, statins have myriad unpleasant, and in some cases acute—or even fatal—side effects, such as many of those Seneff's husband experienced. These include muscle pain, weakness, fatigue, memory and cognition problems, and—as you will soon see—very serious problems with sexual functioning.

The executive summary of what statin drugs do is this: They cut off cholesterol production in the body. That's pretty obvious, right? But to understand why the side effects of this seemingly “innocent” action are so severe and troubling, you have to understand how statin drugs cut down on the body's production of cholesterol. When you do, you'll see that cutting off cholesterol production in the way that statin drugs do is like trying to stop the growth of a branch at the top of a tree by starving the roots at the trunk. The “side effect” of starving the roots is that you destroy the rest of the tree. The irony is that there was no need to remove the branch in the first place.

Besides being far less effective than you've been led to believe, statins have myriad unpleasant, and in some cases acute—or even fatal—side effects.

Let us explain.

Statin Drugs and Your Brain: Memory, Thinking, and Alzheimer's

Cholesterol is synthesized in the liver through a pathway called the *mevalonate pathway*, also known as the *HMG-CoA reductase pathway*. Don't worry about those long names, but do pay attention to what this pathway does. The HMG-CoA reductase enzyme is the one directly responsible for initiating the manufacture of cholesterol, and it is this

enzyme with which the statin drugs interfere. (Statin drugs are technically known as HMG-CoA reductase inhibitors.)

But HMG-CoA reductase is at the base of the mevalonate pathway, much as the trunk of the tree is the base from which all branches grow. In the case of the mevalonate pathway, a lot more branches “grow” than just the cholesterol “branch.” The mevalonate pathway produces cholesterol, but it is also responsible for the production of coenzyme Q₁₀, one of the most vital nutrients for the heart. Cutting off the mevalonate pathway at the root also blocks or lowers the production of nuclear factor kappa B (NF-κB)—more on this in a moment—and disrupts the activities of pathways that regulate the production of tau proteins, dolichols, and selenoprotein.

Now don’t worry. We’re not going to go into all these branches and what they do. Suffice it to say that these are all-important pathways producing all-important compounds for the body, and the long-term effect of messing with such a complicated system is unpredictable at best. But we are going to go into a bit of detail when it comes to four of the actions of cholesterol drugs that may account for the lion’s share of their effects, including, unfortunately, their significant and numerous side effects.

The first of these actions is the most obvious one: Statin drugs lower cholesterol, and they do a great job of it. So good, in fact, that they lower cholesterol in the brain, and that is very far from a good thing.

The brain absolutely depends on cholesterol for optimal functioning. Although the brain makes up only about 2 percent of the total weight of the body, it contains 25 percent of the body’s cholesterol. Cholesterol is a vital part of cell membranes in the brain, and it plays a critical role in the transmission of neurotransmitters. Without cholesterol, brain cells can’t effectively “talk” to each other, cellular communication is impaired, and cognition and memory are significantly affected, usually not in a good way! (See the sidebar, “SpaceDoc: The Strange Case of the Missing Memory.”)

Cognitive and memory problems are one of the most dramatic and frequent side effects of statin drugs, and a 2009 study from Iowa State University demonstrates why. Yeon-Kyun Shin, Ph.D., a biophysics professor in the department of biochemistry, biophysics, and molecular biology at Iowa State, tested the whole neurotransmitter machinery of brain cells in a novel experiment. (Neurotransmitters affect data-processing and memory functions.) He measured how the system released

neurotransmitters when cholesterol was removed from the cells and compared that with how the system functioned when cholesterol was put back in.

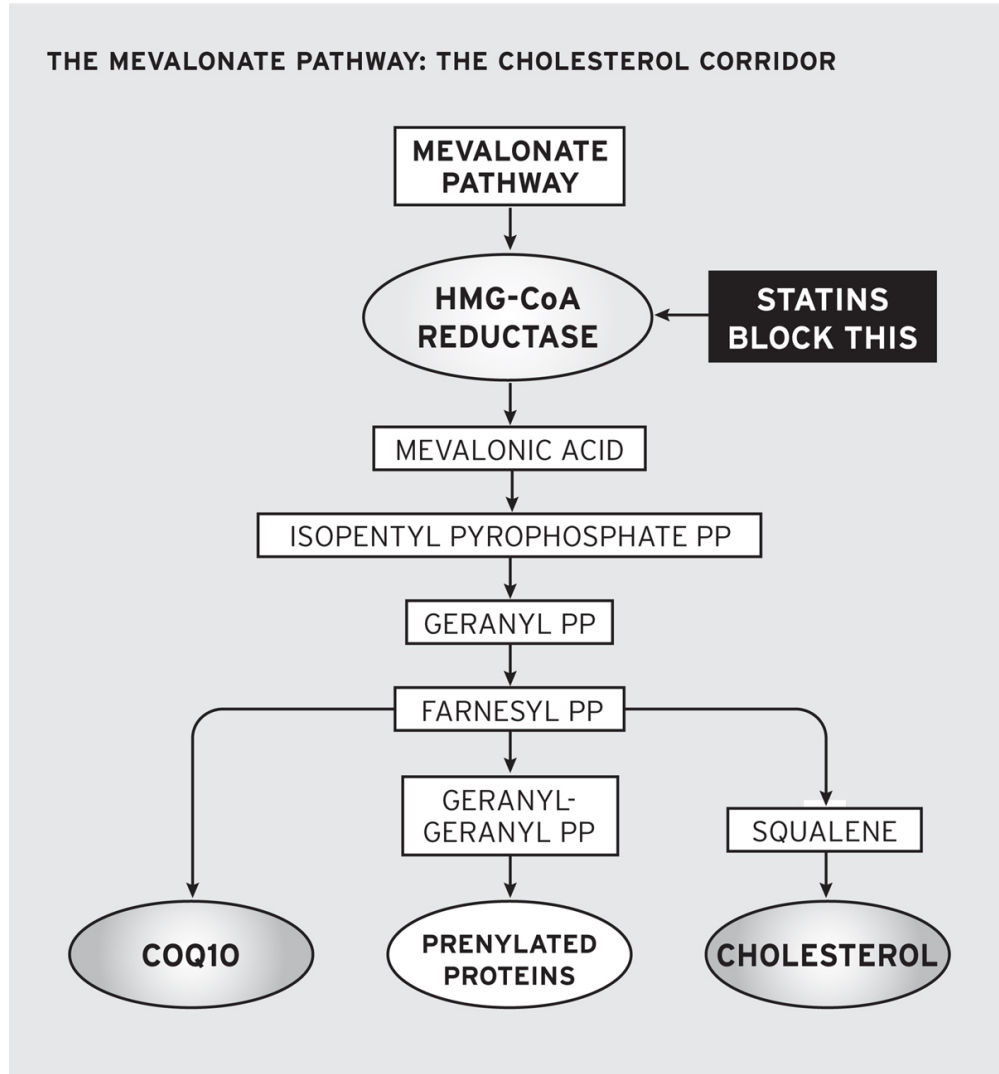


Chart by Michelle Mosher.

Cholesterol increased protein function fivefold.

“Our study shows there is a direct link between cholesterol and neurotransmitter release,” said Shin. “Cholesterol changes the shape of the protein to stimulate thinking and memory.”⁴ In other words—how smart you are and how well you remember things.⁵

Note to parents: Now that you understand this, the fact that some groups are currently advocating statin drugs for children, whose brains aren’t even

fully developed until they're twenty-five, should be as utterly frightening to you as it is to us.

Adults should be no less sanguine. Speaking at a 2008 luncheon discussion put on by Project A.L.S.—a nonprofit dedicated to raising money for brain research and the understanding of Lou Gehrig's disease—the vice chairman of medicine at New York Presbyterian Hospital, Orli Eisinger, M.D., had this to say regarding the number-one-selling statin drug in the world, Lipitor: “This drug makes women stupid.”⁶

Statin Drugs and Your Energy

Here is one noncontroversial and incontrovertible fact: Statin drugs significantly deplete your body's stores of coenzyme Q₁₀ (CoQ₁₀).

If you don't already know what CoQ₁₀ is, this would be a great time to become familiar with it. Once you understand the importance of CoQ₁₀ to human health, you'll immediately appreciate why the depletion of CoQ₁₀ by statin drugs is such a big deal. The depletion of CoQ₁₀ is one of the most important negative effects of statins, and the one that is pretty much responsible for a host of common side effects involving muscle pain, weakness, and loss of energy.

CoQ₁₀ is a vitamin-like compound found in virtually every cell in the human body, and when your CoQ₁₀ levels fall, so does your general health. CoQ₁₀ is used in the energy-producing metabolic pathways of every cell. It's a powerful antioxidant, combating oxidative damage from free radicals and protecting your cell membranes, proteins, and DNA. In a previous book, Dr. Sinatra has referred to CoQ₁₀ as “the spark of life,” and Dr. Jonny has written about it at length in *The Most Effective Natural Cures on Earth*.

Without CoQ₁₀, our bodies simply can't survive.

The production of CoQ₁₀ happens in one of the branches of the mevalonate pathway tree that is blocked by the action of statin drugs. When cholesterol production is interfered with in this way, so is the production of CoQ₁₀. Interestingly, the most important muscle in the body—the heart—contains the greatest concentration of CoQ₁₀. The severe reduction in CoQ₁₀ caused by statin drugs damages not only the heart but also the

skeletal muscles that rely on CoQ₁₀ for energy production. How ironic that a drug given to prevent heart disease—which it barely does, and then only in extremely limited circumstances—substantially weakens the very organ it's meant to protect!

The fact that statin drugs cause depletion of CoQ₁₀ levels has been known for decades. Merck, the manufacturer of Zocor (one of the bestselling statin drugs), has had a patent on a combination statin-CoQ₁₀ drug since around 1990 but never manufactured it. Although no one knows for sure why, it's widely believed that Merck never produced this drug because there was no real economic incentive to alerting the public to the CoQ₁₀ problem and then “solving” it with a combo drug. No one else was doing it, so why should Merck bother?

SPACEDOC: THE STRANGE CASE OF THE MISSING MEMORY

In 2006, magician and performance artist David Blaine decided to do a stunt in which he was immersed in water for seven days. To prepare for this grueling event, he decided to train with a man named Duane Graveline.

Graveline has a particularly interesting resume: He's both an M.D. and an astronaut, one of six scientists selected by NASA for the Apollo program. He's also a renowned expert in the field of zero gravity deconditioning research. The reason Blaine chose him as a consultant was because Graveline himself had once spent seven days immersed in water as part of his own zero gravity conditioning program.

Ask Graveline how terrifying it was to be immersed in water for seven days, and he'd probably tell you it was a walk in the park compared to what he went through when he suddenly lost his memory.

Graveline's story began in 1999, when he took his annual astronaut physical. The doctors said his cholesterol was too high and prescribed Lipitor, the biggest selling drug in the history of medicine.

But shortly after starting the medication, Graveline experienced a six-hour episode of transient global amnesia (TGA). TGA is the medical term for a rare phenomenon that can last anywhere from fifteen minutes to twelve hours. TGA sufferers suddenly lose the ability to retain new memory and often fail to recognize familiar surroundings. Often they can't even identify members of their own family, and they frequently become confused and disoriented. People experiencing TGA will literally regress in time—hours, days, weeks, or even years—and not have any memory of their life after the time they've regressed to.

Following the episode, Graveline discontinued the statin. But during his next physical a year later, he was persuaded to restart the statin at half the previous dose. Two months after doing so, he experienced another episode of TGA. This time it lasted for twelve hours. His awareness was tossed back fifty-six years to when he was thirteen years old—he knew the names of every teacher and kid in his classes, but he had no memory of his subsequent life. He didn't even recognize his

wife, who was with him when the incident occurred. Decades had been erased from his mind as if they had never happened.

Fortunately, the amnesia lifted, and his memory reverted back to normal. He stopped taking the statin again, too—this time for good.

Graveline began his own personal search for the facts about statins, and what he found was more than a little disturbing.

He learned that TGA had befallen hundreds of other patients taking statin drugs. He also discovered that the side effects of statin drugs in general were both potentially serious and vastly underreported—they included elevated liver enzymes, muscle wasting, sexual dysfunction, and fatigue. He began digging a little deeper into the whole issue of statin drugs and heart disease. He started questioning some of the accepted notions about cholesterol, ideas he himself had once embraced wholeheartedly: for example, the idea that cholesterol causes heart disease and the idea that lowering cholesterol is one of the most important things you can do to protect your heart.

“I came to realize that cholesterol was in no way the heinous foe we had been led to believe it was,” he wrote. “Instead, I realized that cholesterol was the most important substance within our bodies, a substance without which life as we know it would simply cease to exist. That billions of dollars have been spent in an all-out war on a substance that is so fundamentally important to our health is undoubtedly one of the great scientific travesties of our era.”³

As we age, we make less CoQ₁₀, so keeping what we have is even more important during our middle-age and older years, when statin drugs are prescribed the most. Lower CoQ₁₀ means less energy production for the heart and muscles. Stephanie Seneff and her associates at MIT collected a large number of subjective reports by patients on various drugs. They gathered more than 8,400 online reviews by patients on statin drugs and compared them for mentions of side effects with the same number of age-matched reviews randomly sampled from a broad spectrum of other drugs.

You can see the comparison of side effects from statin and non-statin drugs in the chart on the opposite page.

To this day, many doctors are completely clueless about the CoQ₁₀ connection and are unaware of its significance. One of us, Dr. Jonny, played tennis for years with a terrific eighty-year-old named Marty. Although in great shape, Marty was always winded, had trouble catching his breath, and frequently experienced muscle pain and fatigue, which he (and his doc) attributed to “getting older.” It turns out that Marty’s doctor had put him on a statin drug for his cholesterol; his symptoms marked a classic case of CoQ₁₀ depletion. When Dr. Jonny pointed this out to him and suggested he immediately start supplementing with CoQ₁₀, Marty said, “I’ll ask my doctor about that!”

PATIENT REPORTS ON STATIN AND OTHER DRUG SIDE EFFECTS

| Side effects | Number statin reviews that mention side effects | Number nonstatin reviews that mention side effects | Associated p-value* (how likely the difference is because of chance) |
|---------------------|---|--|--|
| Muscle cramps | 678 | 193 | 0.00005 |
| General weakness | 687 | 210 | 0.00006 |
| Muscle weakness | 302 | 45 | 0.00023 |
| Difficulty walking | 419 | 128 | 0.00044 |
| Loss of muscle mass | 54 | 5 | 0.01323 |
| Numbness | 293 | 166 | 0.01552 |
| Muscle spasms | 136 | 57 | 0.01849 |

Source: Stephanie Seneff. “How Statins Really Work Explains Why They Don’t Work,” http://people.csail.mit.edu/seneff/why_statins_dont_really_work.html.

* P-value (probability value) is a measure of the likelihood that such results could be found by chance. In statistics, a probability of 0.05 or less means the result would be obtained by chance five (or fewer) times in a hundred. When this happens, statisticians consider the results not to be due to chance. All of the above findings meet this criteria (some of them by a long shot), meaning they are considered statistically significant.

The doctor barely knew what CoQ₁₀ was, was utterly clueless about its importance, and was completely unaware of this critically important side effect of the drug he had prescribed—a drug that is especially unnecessary in this case, because high cholesterol is actually *protective* for older people.

This, folks, is just one example of what we like to call “cholesterol madness.”

If you are on a statin drug and need to remain on one for whatever reason, don’t spend one more day without supplementing with CoQ₁₀. Run, don’t walk, to your nearest pharmacy or health food store and pick some up. We recommend a minimum of 100 mg twice a day, preferably of the ubiquinol form or a highly bioavailable ubiquinone.

Statin Drugs and Immunity (NF-kB)

One of the good things about statin drugs is that they are anti-inflammatory. This is important and probably one of the main reasons statins show any of the benefit they sometimes do. Inflammation, as you learned in [chapter 3](#), is one of four major contributors to heart disease.

We want our anti-inflammatory arsenal to be as powerful as possible, because inflammation is a major component of every degenerative disease known to humankind. Anti-inflammatory foods, supplements, drugs? Bring ‘em on!

So the fact that statins are anti-inflammatory is a good thing. But the way they accomplish this anti-inflammatory action may not be without problems.

One of the compounds made in the mevalonate pathway is something called nuclear factor kappa B, also known as NF-kB. NF-kB is an important part of the immune system, but it is highly inflammatory. (Remember, inflammation is an important part of the healing process, so you need some inflammatory compounds in your body to help fight infectious microbes.) It’s widely believed that the main reason statins are so anti-inflammatory is because they turn down the volume on NF-kB production (just as they turn down the volume on CoQ₁₀ production, another “branch” in the mevalonate pathway that’s short-circuited by statins).

You might well ask how this could be anything but a good thing, right? Statins lower NF-kB, which is an inflammatory chemical, and the less we

have of those the better!

Well, maybe.

Although at first blush it might seem that lowering this powerful inflammatory chemical produces a wholly good effect, the problem is that NF-kB is neither “good” nor “bad.” Some infectious organisms—*E. coli* and salmonella, for example—actually manage to infect the body by inhibiting NF-kB, just as statin drugs do. Other microbes, such as the bacterium that causes chlamydia, actually *enhance* NF-kB. The Epstein-Barr virus inhibits NF-kB at some points in the life of the virus and activates it at other points.

The point is, no one knows the long-range consequences of constantly suppressing NF-kB by cutting off the mevalonate pathway, as statin drugs do. Some of the results—for some people, with some conditions—are indeed positive. Some of the results—for *other* people, with *other* conditions—could be disastrous. There are far easier, safer, and more natural ways to reduce inflammation than by using a drug that has been shown to have a strong link to serious side effects and may—as in the case of long-term suppression of NF-kB—have consequences we don’t even know about yet.

But the impact of cholesterol lowering on the immune system is not limited to the effect on NF-kB. Research has shown that human LDL (the so-called “bad” cholesterol) is itself able to inactivate more than 90 percent of the worst and most toxic bacterial products.⁷

A number of studies have linked low cholesterol to a greater risk for infections. A review of nineteen large, peer-reviewed studies of more than 68,000 deaths found that low cholesterol predicted an increased risk of dying from respiratory and gastrointestinal diseases, both of which frequently have an infectious origin.⁸ Another study that followed more than 100,000 healthy individuals in San Francisco found that those who had low cholesterol at the beginning of the fifteen-year study were far more likely to be admitted to the hospital because of an infectious disease.⁹ And an interesting finding from the MRFIT study found that sixteen years after their cholesterol was first checked, the group of men whose cholesterol level was 160 or under were four times more likely to die from AIDS than the group of men whose cholesterol was over 240!¹⁰

STATINS FOR CHILDREN?

Dr. Sinatra will sometimes—not often, but sometimes—prescribe a statin drug for people in this specific population: middle-aged men who have already had a heart attack or have documented coronary artery disease. Both of us believe there is no other good use for statin drugs. They definitely should not be prescribed for most women, they do not need to be prescribed for people who have not had a heart attack, and they definitely—emphatically, positively—should not be prescribed for children.

We want to clarify this position once again, partly to help counteract the enormous lobbying efforts of the pharmaceutical companies, which, as of this writing, are working tirelessly to expand the market for statin drugs to include children, one of the worst ideas in history. In *The End of Illness*, author David Agus, M.D., recommends that everyone in the country be on a statin drug. Agus is well-meaning but completely wrong. His idea, if accepted, may be the next medical disaster just waiting to happen.

So a middle-aged man who has already had a first heart attack may indeed find that a statin drug, along with coenzyme Q₁₀ and fish oil, fits into his overall treatment plan.

For anyone else, proceed with caution!

Statin Drugs and Your Sex Life

And now for the part that no one is talking about. The dirty little secret about statin drugs. Please don't shoot the messengers. Ready?

Statin drugs have a terrific ability to completely mess up your sex life. No kidding.

Not only is this a common side effect of cholesterol lowering, but it's also vastly underreported. And worst of all, many people who experience sexual dysfunction, especially men, have no idea that it might very well be related to the drug they're taking to lower their cholesterol.

Erectile dysfunction affects more than half of all men between the ages of forty and seventy years.¹¹ We've already seen how lowering cholesterol can have serious consequences for memory, thinking, and mood. Just as the brain needs cholesterol for neurotransmitters to properly function, the gonads need it to produce the hormonal fuel to keep our sex lives humming. All the major sex hormones—testosterone, progesterone, and estrogen—come from cholesterol. It's utterly preposterous to assume that lowering cholesterol, which is tantamount to downsizing your body's own sex hormone factory, is not going to have a profound effect on sexual functioning.

Of course it is. And it does.

Several studies have shown beyond any doubt that statin drugs lead to a reduction in sex hormones, most notably testosterone.¹² And this is a very big deal indeed.

Remember, low testosterone is not just a male problem—women also make testosterone (albeit much less of it), and it's increasingly clear that even this small amount of testosterone strongly influences women's sexual desire. (Most anti-aging clinics now routinely prescribe small, physiologic doses of testosterone to postmenopausal women to treat sagging libido levels and improve general well-being. Testosterone is vitally important to both sexes!)

We know for sure that low cholesterol is linked to low testosterone in women from studies conducted on women with a condition known as polycystic ovary syndrome (PCOS). Women with PCOS suffer from an abnormal increase in their testosterone levels, but when you lower their cholesterol their testosterone plummets, leaving little doubt about the anti-hormone effect of statin drugs.¹³ The effect on men is pretty easy to document, and many studies have done just that. One study showed that Crestor, one of the most popular statin drugs, increased the risk of erectile dysfunction at least two and up to seven times!¹⁴

If libido and sexual health were the only things disturbed by diminishing levels of testosterone, that would be reason enough to be deeply concerned. But low testosterone has a much more global influence on overall health. Low testosterone is associated with decreased life expectancy, as well as

increased risk of mortality from cardiovascular disease.¹⁵ And for those who have testosterone levels below a certain threshold, the risk is doubled!

As important as it is, testosterone certainly isn't the only driver of sex and desire in either males or females. Another important hormone—known as the “hormone of love”—is oxytocin.

Oxytocin is produced in the brain, and levels are very high during childbirth and nursing because one of its functions is to help the mother bond with the child. When you cuddle after sex, you're flooded with oxytocin. (Males also make oxytocin, just a lot less of it than females do.) Researchers love to study male prairie voles because they are a rare exception to the male–female oxytocin dichotomy; male prairie voles, unlike males of most species, make a ton of the stuff. Male prairie voles are also a rare example of monogamy in the animal kingdom, and this has long been attributed to their oxytocin production, resulting in fairly permanent “pair-bondings.” The bottom line is that oxytocin, which helps you feel good and bond with another person (or another prairie vole!), is an important part of human sexual desire, expression, and satisfaction.

So what does oxytocin have to do with cholesterol?

Unlike testosterone, oxytocin is not made from cholesterol. But oxytocin gets into its target organs via cell receptors, and those cell receptors are highly dependent on cholesterol-rich membranes. Critically important parts of the membranes known as lipid rafts don't work well without cholesterol, meaning that lowering cholesterol interferes with the ability of hormones such as oxytocin to reach their destination and work their magic. (As we've seen, this also happens with neurotransmitters in the brain that depend on cholesterol-rich membranes for cellular communication.)

Finally, statins also interfere with serotonin receptors in the brain.

In case you're not familiar with serotonin, it's one of the critical neurotransmitters involved in mood. The most commonly used antidepressants, including the blockbuster drugs Prozac, Zoloft, Lexapro, and the like, are known as *selective serotonin reuptake inhibitors* (SSRIs) because they act mainly to keep serotonin hanging around the brain longer. Serotonin has a great deal to do with our feelings of relaxation, well-being, and satisfaction.

So how exactly do statins act on the physiology of serotonin?

Simple. Much like oxytocin (discussed above), serotonin depends on cell receptors to get into the cells. Serotonin receptors—just like oxytocin receptors—are anchored into the cholesterol-rich lipid rafts in the cell membrane. If you lower cholesterol you’re going to interfere with serotonin getting into the cells. It’s that simple. In fact, research has convincingly demonstrated that serotonin receptors can be rendered dysfunctional by statin drugs.¹⁶

The noted French researcher Michel de Lorgeril, M.D. (lead author on the Lyon Diet Heart Study), is so strongly convinced that statins are screwing up our sex lives that he devoted an entire book to the subject. His only book in English, it offers a brilliant argument supported by ninety-two references from peer-reviewed journals and textbooks. The name of the book—*A Near-Perfect Sexual Crime: Statins Against Cholesterol*—pretty much tells you what de Lorgeril thinks about statins and our sex lives.

Statins and All-Cause Mortality, Diabetes, and Cancer

Earlier, we discussed how the majority of cholesterol-lowering studies didn’t show any difference in death rates between patients who took cholesterol-lowering meds and patients who didn’t. In some of these cases, a slight reduction in heart disease deaths was clearly offset by a slight increase in deaths from other causes, so the overall net “gain” in terms of lives saved was a big fat zero.

But studies show even more troubling results. For example, a study in the *Journal of Cardiac Failure* showed that low cholesterol was actually associated with a marked increase in mortality in heart failure cases.¹⁷ And the Italian Longitudinal Study on Aging, published in the *Journal of the American Geriatric Society*, found that those with cholesterol levels lower than 189 were far more likely to die than those with the highest cholesterol levels. The researchers concluded, “Subjects with low total cholesterol levels are at higher risk of dying even when many related factors have been taken into account,” adding that “. . . physicians may want to regard very low levels of cholesterol as potential warning signs of occult disease or as signals of rapidly declining health.”¹⁸

There are also troubling indications that statin drugs may be associated with a higher risk for cancer and diabetes, though the evidence is far from conclusive. Researchers from the Department of Medicine at Tufts Medical

Center and Tufts University School of Medicine examined twenty-three statin trials looking for any connection between cholesterol levels and cancer. They concluded that “the risk of cancer is significantly associated with lower achieved LDL-cholesterol levels,” adding that “the cardiovascular benefits of low achieved levels of LDL-cholesterol may in part be offset by an increased risk of cancer.”¹⁹ Further, a meta-review of five statin trials found that an increased risk of diabetes was associated with “high-dose” statin therapy.²⁰ This finding was also seen in the well-known JUPITER trial, about which we’ll have a lot more to say in a bit.

Remember Duane Graveline? The astronaut medical doctor who came down with transient global amnesia as a result of statin drug use? Graveline has spent the past decade or so accumulating data on statin side effects. Hundreds if not thousands of people have written to Graveline detailing their side effects with statin drugs, and his website contains dozens of essays on these various syndromes, conditions, and side effects.²¹ In addition, Teresa Graedon, Ph.D., and Joe Graedon, M.S., authors of the popular *The People’s Pharmacy*, have published a number of letters from readers on their website regarding statin side effects. Three examples:

“I have been on cholesterol-lowering medication for some time. I had been telling my doctor that my medication was doing something to my muscles and he would not believe me. I changed doctors and the new one discovered that my muscles’ enzymes were 800 (normal is 200). He took me off the medication and my enzymes came down. When I went on a different statin, they climbed back up again.”²²

“My doctor insists I must take statins to lower my cholesterol even though I experience pain with all of them. Sometimes the pain gets so bad that I struggle not to cry when I walk down the hall of my child’s school. My doctor says I should accept ‘a little discomfort.’ He says this pain is rare but I know a lot of people who have had the same muscle pain.”²³

“I have taken Lipitor for several years. I now notice numbness in my feet and sporadic memory loss, difficulty balancing my checkbook and using the computer. I have a Ph.D., so this is alarming. My doctor says Lipitor is not to blame. My cholesterol is great and not to stop. Is there any evidence that Lipitor could be connected to these symptoms?”²⁴

Okay, so it's pretty clear that statin drug side effects are hardly uncommon. But if so many people have so many symptoms as a result of taking statin drugs, why, you might well ask, have you not heard about them? Don't doctors know about this stuff?

Interesting question. And one that was exhaustively investigated in a groundbreaking study by Beatrice Golomb, M.D., Ph.D., who wanted to find out exactly how doctors routinely handled patient reports of statin side effects.²⁵ What she found was disturbing: A comfortable majority of doctors dismissed the complaints. Patients in the study described symptoms of muscle pain, tightness, cramping, or weakness to a total of 138 doctors, 62 percent of whom dismissed the possibility that the symptoms were related to statins. Patients presented symptoms of nerve injuries, known as neuropathies, to 49 physicians, 65 percent of whom dismissed the possibility that the symptoms were statin-related. And they presented symptoms of impaired thinking or memory to 56 doctors, a whopping 71 percent of whom dismissed any possibility of a relationship to the meds!²⁶

This research is important for many reasons, but there's one in particular that's worth mentioning: If docs aren't acknowledging these symptoms—known as *adverse effects*—that means they're also not reporting them to MedWatch, the Food and Drug Administration's reporting system for adverse events. Virtually every doctor we know who is knowledgeable about this believes that the side effects of statin drugs are deeply underreported, a fact that should concern all of us (though it certainly doesn't cause the drug companies to lose any sleep).

Okay, we've answered the first question—"What are the risks?"—in our two-question inquiry. Now it's time to take a look at the second question: "What are the benefits?" Only then can we make an intelligent decision about the risk-benefit ratio and decide whether it really makes sense to take (or stay) on a statin drug.

Let's go to the proverbial videotape.

THE “BENEFITS” OF STATIN DRUGS: NOT EXACTLY WHAT WE’VE BEEN LED TO BELIEVE

To understand how you may have been misled about the benefits of statin drugs, it’ll be useful to first understand something about how it’s possible to mislead with numbers.

Imagine, if you will, that you are on a game show and the host asks you, “Would you rather have 90 percent of the money behind door number one, or 10 percent of the money behind door number two?” All things being equal—that is, if there were the same amount of money behind both doors—you’d pick the 90 percent option. But that wouldn’t be much of a game show, would it? The point is that unless you know how much money is behind the doors, it’s impossible to know the real significance of the 90 percent and the 10 percent. Obviously, you’d choose 10 percent of \$1 million over 90 percent of \$100.

So we must know the real, *absolute* amount of anything if we’re to evaluate its significance. The *percent alone* is a kind of meaningless number unless you know what it’s a percentage *of*.

Suppose we choose 90 percent of the money behind door number one and find \$100 there. You can refer to your take-home haul as “90 percent of the total,” or you can refer to it as \$90. Both are accurate, but the first (90 percent) is misleading. (It reminds us of what Jack, Dr. Jonny’s wisecracking tennis partner, says when the score is 2 to 1: “I’ve got a 100 percent lead over you!”)

When you refer to your take-home money as “90 percent” you are expressing the amount in relative terms. Relative to the whole, your \$90 is, in fact, 90 percent. Sure sounds like a lot, doesn’t it? But when you refer to your take-home money as \$90, you are expressing the real amount in absolute terms. Ninety dollars is the actual, *real* amount of money we’re talking about here. Who cares what percentage it was?

Absolute and relative. Hold that thought.

Now there’s a parallel concept to absolute and relative amounts that’s used in clinical studies all the time. It’s called absolute versus relative risk.

One—the absolute risk—is the real, true reduction in risk that you get when you take, for example, a drug that is reputed to help prevent heart disease. That’s the number you really want to know. The other—the relative risk—is a big smokescreen that *obscures* what you really want to know, just like “90 percent of the money behind door number one” *sounds* like a lot but really isn’t.

Here’s an illustration of what we’re talking about. Let’s say you’re a gambler, and you are offered the chance to buy a special magic wand that guarantees you a 100 percent increase in your chance of winning the lottery. This sounds like a really good deal, right? But remember, it’s a relative number. To evaluate your real chances of winning the lottery, we have to look at the *absolute* numbers. Your normal chance of winning the lottery without that magic wand is 1 in 87,000,000, so the magic wand just upped your chances to 2 in 87,000,000. Whoop-de-doo. Sure, it’s a *100 percent improvement*, which sounds impressive, but *so what?* You still have virtually *no chance* of winning the lottery, and you’re out of pocket for the cost of the wand. It’s like having 90 percent of a “fortune” that’s only worth a dollar.

The above example may seem silly, but it illustrates exactly what researchers do to make their results seem more dramatic, particularly when those research results are being used to tout the benefit of a drug. (Remember, most drug companies fund their own studies. Many if not most of these studies wind up being little more than marketing materials for the drugs being studied, wrapped up in the guise of science.) The researchers use percentages, specifically percentages that make the results sound far more impressive than they actually are. Yes, what they say is technically true—just as it’s true that the magic wand offers you a 100 percent increase in your lottery chances—but it’s wholly misleading. A more accurate way to express what you’ve bought with the magic wand is to say your chances went from 1 in 87,000,000 to 2 in 87,000,000. Forget the “100 percent increase”—what really happened is you went from *one* chance in a zillion to *two* chances in a zillion. Not something you’d probably pay a lot of money for.

Fuzzy Math, Anyone?

Now let's see how the drug companies use the same misleading "relative" numbers to mislead you about the effects of their drugs.

The makers of Lipitor, for example, famously advertised a 33 percent reduction in heart attack risk in their magazine ads. But read the fine print. It's a relative number. Here's how it's computed. Let's say you have a hundred randomly chosen men who are not taking medication; and let's say that out of that hundred, it's statistically likely that three of them would be expected to experience a heart attack at some point over the course of five years—in other words, 3 percent of the total number of men (one hundred) would be expected to have a heart attack.

Now, if you had put those same men on Lipitor over the course of the same five years, only two would be expected to have a heart attack (2 percent of the total number of men). A reduction from three heart attacks to two heart attacks is in fact a 33 1/3 percent reduction in relative risk, but the real, *absolute* number of heart attacks prevented is only *one*. One heart attack among a hundred men over the course of five years. The real *absolute reduction in risk* is 1 percent (the difference between the 3 percent in the no-drug group who would have had a heart attack and the 2 percent in the Lipitor group). The "33 percent reduction" figure is, again, a relative number, and because it's way more impressive than the much more truthful "1 percent" (the absolute number), researchers frequently choose to use relative risk instead of absolute risk when they report results! (Doesn't it sound much better to say Lipitor reduces risk by 33 percent than to say Lipitor reduces heart attack risk from 3 percent to 2 percent?)

Keep this in mind when you read our review of some of the studies used to promote the idea that statins save lives.

There's a second concept that would be helpful to understand before we venture into the studies themselves, and that's the distinction between *primary prevention* and *secondary prevention*. Primary prevention refers to treating people who have not had a heart attack for the purpose of preventing one. Secondary prevention refers to treating people who've already had a heart attack for the purpose of preventing another. As you'll soon see, the effect of statins on these two populations is quite different.

Before we get to that, there's something else you should know about study interpretation in general that may help you make more sense out of some of the statin propaganda. Studies usually produce a mass of data that

can be spun in a number of ways. Let's take one common substance we're all familiar with: alcohol. There are no shortages of studies demonstrating that moderate alcohol consumption lowers the risk of heart disease. So far, so good. But those same studies have also teased out a troubling connection—alcohol consumption increases the risk for breast cancer! Both facts—that alcohol helps your heart and that alcohol increases the risk for breast cancer—are absolutely true, but if you're a manufacturer of alcoholic beverages you're going to be talking up the reduction in heart disease risk and not calling attention to the association with breast cancer.

In much the same way, a drug company-sponsored study might indeed find a beneficial effect on heart disease associated with a particular drug, a beneficial effect similar to that of alcohol. But if in addition to lowering the risk for heart disease the drug increased the risk for diabetes—a finding that's shown up in a couple of statin drug studies—that finding might easily be buried in the text where only the most determined investigators would be likely to uncover it.

Now that you understand these concepts—relative versus absolute percentage, primary versus secondary prevention, and burying inconvenient associations where they are less likely to be noticed—let's look at some representative studies on statin drugs and see what they *really* say, as opposed to what their manufacturers would like you to *think* they say.

The ALLHAT Study: Not a Single Life Was Saved

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), conducted between 1994 and 2002, was the largest North American cholesterol study ever undertaken, and as of 2002, it was the largest study ever done using the statin drug pravastatin (brand name Pravachol). Ten thousand participants with high LDL cholesterol levels were divided into two groups. One group was treated with pravastatin, and the other group was simply given the standard advice on “lifestyle changes.”

Twenty-eight percent of the pravastatin takers did lower their cholesterol by a small but statistically significant amount (compared to 11 percent who did so in the “lifestyle change” group). This allowed the pravastatin folks to trumpet a significant reduction in cholesterol and declare the trial a success.

Not so fast.

When the death rates from heart attack were examined, there was no difference between the two groups. The statin drug lowered cholesterol in 28 percent of the people taking it, but not a single life was saved. Pravastatin neither significantly reduced “all-cause” mortality (death from any reason whatsoever), nor reduced fatal or nonfatal coronary heart disease in the patients who took it.²⁷

The ASCOT-LLA Trial: Not Exactly a Slam Dunk for Lipitor

The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) was a multicenter randomized controlled trial in which more than ten thousand patients with high blood pressure and at least three other cardiovascular risk factors were assigned to one of two groups. Half were given Lipitor, half were given a placebo (an inactive substance in a pill form). Remember, too, that all patients in this study were hypertensive. Most were overweight (average BMI 28.6), 81 percent were male, and about a third were smokers.

In this study, even after a year, those taking Lipitor saw clear benefits, though as we’ve pointed out, this may be because of the many other things statin drugs do besides lower cholesterol. And the folks in this study certainly had risk factors (e.g., being overweight, having high blood pressure, etc.), so any one of the positive effects of statin drugs (e.g., its antioxidant, blood-thinning, or anti-inflammatory qualities) could easily have made a difference. Sure enough, fatal and nonfatal strokes, total cardiovascular events, and total coronary events were all significantly lowered.

Sounds like a slam dunk for Lipitor, doesn’t it?

Well, maybe.

After three years, there was no statistical difference in the number of deaths between the two groups. (In fact, there were actually a few more deaths among the women taking Lipitor than among the women taking the placebo.) So approximately \$100 million was spent, and not a single life was saved.

Worth noting: Of the fourteen authors credited in the ASCOT-LLA study, all of them served as consultants to—and received travel expenses, speaking fees, or research funding—from pharmaceutical companies

marketing cholesterol-lowering drugs, including Merck, Bristol-Myers Squibb, AstraZeneca, Sanofi, Schering-Plough, Servier, Pharmacia, Bayer, Novartis, and Pfizer. Pfizer (maker of Lipitor) was the principle funding source for the study. That fact alone certainly doesn't make the results invalid, but it's still worth mentioning.

The Heart Protection Study: Pretty Weak Protection

The Heart Protection Study (HPS) divided more than twenty thousand adults with either coronary artery disease or diabetes into two groups and gave one group 40 mg of the statin Zocor daily while the other group received a placebo.²⁸ It was claimed that “massive benefits” were obtained by lowering cholesterol with the statin drug, and indeed fewer people died in the Zocor group than in the placebo group.

But let's look at the absolute numbers. Those in the Zocor group had an 87.1 percent survival rate after five years, but those in the placebo group had an 85.4 percent survival rate, an absolute difference of 1.8 percent. Most important, the survival rates were independent of lowering cholesterol. In other words, lowering LDL levels made essentially no difference in the risk of death from heart disease. (This is not difficult to understand when you factor in the other things statins do besides lower cholesterol. If anything, it simply shows that statin drugs may be useful in certain populations, but if they are, it's independent of their ability to lower cholesterol. In fact, it increasingly looks like lowering cholesterol may be the least significant thing statins do.)

As Uffe Ravnskov, M.D., Ph.D., stated in a letter to the editor of the *British Medical Journal* regarding the Heart Protection Study results, “Tell a patient that his chance not to die in five years without statin treatment is 85.4 percent and that [statin] treatment can increase this to 87.1 percent. With these figures in hand I doubt that anyone should accept a treatment whose long-term effects are unknown.”²⁹

Japanese Lipid Intervention Trial: No Relationship between LDL and Dying

In this trial, more than forty-seven thousand patients received Zocor over the course of six years. There was quite a variety in their response to this

treatment. Some folks saw dramatic lowering of their LDL levels, some saw a moderate fall in their levels, and some experienced essentially no reduction in their levels.

After five years, the researchers examined the death rate among the participants and cross-referenced these deaths with the patients' LDL levels. You'd think this would be the perfect study to demonstrate a correlation between lower LDL levels and a decreased risk for heart disease, right? Clearly, those whose LDL levels had dropped dramatically would have been far more likely to live, while those whose cholesterol levels had not dropped at all would have been far more likely to die, and those who had lowered their cholesterol only a modest amount would have fallen somewhere in between.

We're sure that's what the researchers expected to see.

But they didn't.

After five years there was exactly no correlation between LDL levels and death rate in the three groups. In other words, whether your cholesterol had been lowered or not had no correlation to whether or not you died. Patients with the highest levels of LDL died at pretty much the exact same rate as patients with the lowest LDL levels (and as patients with LDL levels in between the highest and the lowest). Bottom line: Lowering LDL levels didn't give you even a drop of protection against dying.

PROSPER: Some Benefits, but Only for Certain People

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was interesting for a number of reasons. In this study, older patients were divided into two groups. The first group consisted of patients with no history of heart disease (primary prevention group), and the second group consisted of patients with current or past cardiovascular disease (secondary prevention group). Half of each group received Pravachol (a statin drug), while the other half received a placebo.

There was some reduction in heart attacks or strokes, but only in the secondary prevention group (those who had current heart disease or a history of heart disease). There was, however, no reduction in heart attacks or strokes in the primary prevention group, the group that had no history of

heart disease to begin with. This is pretty much in keeping with the findings of the vast majority of other studies.

But there were two other interesting findings, one of them quite troubling.

When pharmaceutical reps spin the data from the PROSPER study, they concentrate on the single fact that Pravachol reduced heart attacks and strokes (while downplaying the fact that it did so only in the group that already had heart disease). Okay, that's good; the prevention of a few heart attacks and strokes, even in a limited population, is always nice. But what about other measures of health, disease, and well-being besides heart attacks and strokes?

To answer this question, researchers decided to look at other measures of total health impact. They looked at “total deaths” and “total serious adverse events” and found that both were completely unchanged by Pravachol. Once again, a statin drug had a beneficial effect on heart attacks and strokes in the secondary prevention population but not in the primary prevention population, and once again, not a single life was saved overall.

The second finding was more troubling. Both groups receiving Pravachol had an increased risk of cancer. Amazingly, the investigators simply dismissed this statistically significant finding as “the play of chance.”

The JUPITER Trial: “Flawed”

We saved this one for last, because it's the juiciest, most perfect example of utter cholesterol madness, media hype, behind-the-scenes manipulation, and intellectual dishonesty.

If you read the papers or watched the news in 2009, you probably heard about this study, though you may not have known what it was called. Its name—JUPITER—stands for the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin. (Even the title of the study should give you pause; you don't do a study to justify the use of a drug you've already decided to use. What if the results of the study indicated the opposite? An objective scientific study wouldn't know the results in advance.)

Anyway, on to the study, about which there's much to dislike and critique—for example, everything.

The JUPITER trial looked at nearly eighteen thousand people whose cholesterol was perfectly normal or even on the low side. What these folks did have, however, were elevated levels of C-reactive protein (CRP). As we've said, CRP is a general measure of inflammation, and for the record, it's a measure we consider important. (You'll read more about CRP testing in [chapter 9](#).) Now it's abundantly clear that what the manufacturers of the drug were aiming for here was a demonstration that statin drugs help prevent deaths even in people with normal cholesterol!

So here's the party line on the JUPITER trial, the line that was robotically repeated in virtually every news outlet in America: The JUPITER trial was such a resounding success that they had to stop it early because it would be “unethical” to continue, given that the group being treated with the drug (Crestor) experienced half as many deaths, strokes, and heart attacks as the control (untreated) group.

The JUPITER trial was touted everywhere as proof that the cholesterol guidelines needed to be changed. Clearly, the drug manufacturers argued, people who met or exceeded the existing standards for cholesterol were demonstrably helped by lowering their “normal” cholesterol even further, virtually cutting their risk for all kinds of terrible things in half! Obviously, they argued to anyone who would listen, we need to make the recommended “normal” levels even lower! (Can you imagine the cheers that would erupt at stockholders' meetings if your product just expanded its market by roughly eleven million people?³⁰ Why that's almost as good as expanding an adult market by targeting children! Oh, that's right. As of 2011, that's what the statin lobbyists were doing. Never mind.)*

Well that was then. This is now.

Nine respected authors, including a Harvard Medical School faculty member, teamed up to write a critical reappraisal of the JUPITER trial, a reappraisal that was published in 2010 in *Archives of Internal Medicine*, one of the most respected, and conservative, medical journals in the world.³¹ “The trial was flawed,” they wrote. “It was discontinued (according to pre-specified rules) after fewer than two years of follow-up, with no differences between the two groups on the most objective criteria.” The authors also said, “The possibility that bias entered the trial is particularly concerning

because of the strong commercial interest in the study.” They concluded that “[t]he results of the trial do not support the use of statin treatment for primary prevention of cardiovascular diseases.”

So how did this study manage to garner headlines like this one: “Heart Attack Risk Lowered More Than 50 Percent by Taking Crestor!”?

Let’s take a look.

The JUPITER trial took 17,800 people—men over sixty, women over fifty—and put them into two groups. One group received 20 mg of Crestor daily, while the other group received a placebo.

Now before we tell you the results, let’s recall the distinction between relative versus absolute numbers, a distinction we talked about earlier.

The study went on for 1.9 years, and at the end of that time it was determined that the risk of having a heart attack in the placebo group was 1.8 percent, while the risk of having a heart attack in the Crestor group was 0.9 percent.

So, yes, there was a 50 percent reduction in risk! Relatively speaking. But let’s do the math on the number that really matters, the absolute risk.

The placebo group had a 1.8 percent risk, and the Crestor group had a 0.9 percent risk, so the absolute, real reduction in risk was 1.8 minus 0.9, or 0.9 percent. In absolute numbers, this means that if you took a group of 100 untreated people, 1.8 of them would have a heart attack at some point over the course of almost two years. If you took that same group of 100 people and treated them all with Crestor for the same period, 0.9 of them would have a heart attack. Researchers calculate that this translates into 120 people needing treatment for 1.9 years in order to prevent one event. At a cost of well over a quarter of a million dollars for almost two years’ worth of Crestor, that’s an awful lot to spend to prevent one event. Especially when there’s a significant chance of experiencing really bad side effects from the medicine that’s costing you a fortune.

Commenting on the JUPITER study in the *New England Journal of Medicine* in November 2008, Mark A. Hlatky, M.D., wrote: “[A]bsolute differences in risk are more clinically important than relative reductions in risk in deciding whether to recommend drug therapy, since the absolute benefits of treatment must be large enough to justify the associated risks and costs.” He added that “[l]ong-term safety is clearly important in

considering committing low-risk subjects without clinical disease to twenty years or more of drug treatment.”³²

WHAT ABOUT PLAQUE?

Okay, so maybe statin drugs don’t cut the risk of dying, except possibly in middle-aged men with previous histories of heart disease (and even then the effect is modest). But what about plaque? Doesn’t aggressive lowering of LDL cholesterol at least reduce plaque? (This could, you might argue, have a positive long-term effect on quality of life, even if it doesn’t actually save lives.)

Well, no.

A study published in the *American Journal of Cardiology* in 2003 used electron beam tomography to evaluate plaque in 182 patients after 1.2 years of treatment with either statins alone or statins in conjunction with niacin.³⁴ And yes, just like in many other studies, cholesterol did indeed go down in those patients treated with cholesterol-lowering medication. But plaque?

Sorry.

The authors wrote, “Despite the greater improvement in [cholesterol numbers] . . . there were no differences in calcified plaque progression.” In fact, subjects in both groups had—on average—a 9.2 percent increase in plaque buildup. “[W]ith respect to LDL cholesterol lowering, ‘lower is better’ is not supported by changes in calcified plaque progression,” concluded the authors.

Did we mention that there was a significantly higher incidence of diabetes in the group treated with Crestor?³³ (In her studies on statin side effects, Stephanie Seneff also observed a highly significant correlation— $p = 0.006$ —between mentions of diabetes and statin drug side effect reports.)

THE DARKER SIDE OF CHOLESTEROL LOWERING

Now, if you're still on the cholesterol-lowering/statin bandwagon, you might be forgiven for trying to look on the bright side. "Look," we can almost hear you saying, "maybe you guys are right. Maybe lowering cholesterol doesn't matter all that much. But clearly there are some good things statins do besides lower cholesterol, as you yourselves have pointed out. They're anti-inflammatory, they're powerful anti-oxidants, and they thin the blood. So what's the harm if people take them?"

Statins are being prescribed left and right to people who have absolutely no business being on them, and to populations for which they have shown no real benefit.

Fair enough. For some people, especially middle-aged men who've already had a first heart attack, the good statins do may indeed outweigh the risks. The problem is twofold: One, statins are being prescribed left and right to people who have absolutely no business being on them, and to populations for which they have shown no real benefit. Two, the risks are significant, serious, varied, and highly underpublicized.

Before we get to our evaluation of the risks and benefits of statin drugs, let's review exactly what it is that cholesterol does in the first place. Understanding the functions of this much maligned molecule will help you understand why so many things can go wrong when we pursue lower and lower cholesterol numbers.

Cholesterol is a hormone factory. Cholesterol is actually the parent molecule for the whole family of hormones known as *steroid hormones*. These hormones include cortisol (known as the fight-or-flight hormone) and the entire family of sex steroids, including estrogens, progestogens, and testosterone. (No wonder statins produce such serious sexual side effects!)

Cholesterol is used by the body to synthesize bile acids. Bile acids are vitally important for the digestion of fat. The acids are synthesized from cholesterol and then secreted into the bile. Bile acids are so important to the body that the body holds on to most of them. It keeps them from being lost in the feces by causing them to be reabsorbed from the lower intestine, put into a kind of “metabolic recycling” container, and taken back to the liver. Still, even with its best efforts, the body loses some bile acids. To make up for this, the liver synthesizes approximately 1,500 to 2,000 mg of new cholesterol a day (that’s about seven to ten times the amount in a large egg). Clearly, the body thinks you need that cholesterol.

Cholesterol is an essential component of all the cell membranes in the body. It’s especially important in the membranes of the brain, the nervous system, the spinal cord, and the peripheral nerves. It’s incorporated into the myelin sheath, a kind of insulation or “cover” for the nerve fibers that facilitates nerve impulse transmission. And, as we’ve already seen, cholesterol is an integral part of the lipid raft, essentially allowing for cellular communication. (That’s why there are so many cognitive problems associated with aggressive cholesterol lowering.) Cholesterol is also important for stabilizing cells against temperature changes.

Cholesterol is important for the immune system. Cholesterol has an important connection to the immune system. Research has shown that human LDL (the so-called “bad” cholesterol) is able to inactivate more than 90 percent of the worst and most toxic bacterial products.³⁵

A number of studies have linked low cholesterol to a greater risk of infections. One review of nineteen large, peer-reviewed studies of more than 68,000 deaths found that low cholesterol predicted an increased risk of dying from respiratory and gastrointestinal diseases, which frequently have an infectious origin.³⁶ Another study that followed more than 100,000 healthy individuals in San Francisco found that those who had low cholesterol at the beginning of the fifteen-year study were far more likely to be admitted to the hospital because of an infectious disease.³⁷ And an interesting finding from the MRFIT study showed that sixteen years after their cholesterol was first checked, the group of men whose cholesterol level was 160 mg/dL or lower was four times more likely to die from AIDS than the group of men whose cholesterol was higher than 240 mg/dL!³⁸

We make vitamin D from cholesterol. It's almost impossible to overstate how important the cholesterol–vitamin D connection is. Vitamin D, which is actually a hormone, not a vitamin, is made from cholesterol in the body. If you lower cholesterol indiscriminately, it stands to reason that you may negatively affect vitamin D levels. And that's hardly insignificant.

Virtually every health practitioner worth his or her salt will tell you that massive numbers of people in the United States (and probably the world) have less than optimal vitamin D levels. According to the Centers for Disease Control and Prevention, “only” 33 percent of the U.S. population is at risk for either vitamin D “inadequacy” or vitamin D “deficiency,”³⁹ but the levels considered “sufficient” are still being debated, and “sufficient” is hardly “optimal.”

In 2010, the Life Extension Foundation conducted a survey of its members—a self-selected sample of people who really care about these things and pay particular attention to their health, blood tests, and supplementation—and found that even in this highly health-conscious population, a whopping 85 percent had blood tests with vitamin D levels below 50 ng/mL, considered the low end of “optimal” (50 to 80 ng/mL).⁴⁰

Why does this matter? Because there is compelling research that links less than optimal levels of vitamin D with heart disease, poor physical performance, osteoporosis, depression, cancer, difficulty in losing weight, and even all-cause mortality. Vitamin D is so important that Dr. Gregory Plotnikoff, medical director of the Penny George Institute for Health and Healing, Abbott Northwestern Hospital in Minneapolis, recently commented, “Because vitamin D is so cheap and so clearly reduces all-cause mortality, I can say this with great certainty: Vitamin D represents the single most cost-effective medical intervention in the United States.”⁴¹

Undoubtedly, there are multiple reasons why so many people are walking around with suboptimal levels of vitamin D, not the least of which is that we are so darn sun-phobic that we now slather SPF 90 on our skin just to go to the grocery store. But is it a coincidence that vitamin D deficiencies and insufficiencies are showing up all over the place at the same time that 11 million to 30 million Americans are on statin drugs, the purpose of which is to lower the very molecule that gives “birth” to this vitally important nutrient?

An Overall Health Benefit of Zero

So what to make of all this? Therapeutics Initiative—a group whose mission is to provide physicians and pharmacists with up-to-date, evidence-based, practical information on prescription drug therapy—wondered the same thing.

Therapeutics Initiative was established in 1994 by the Department of Pharmacology and Therapeutics in cooperation with the Department of Family Practice at the University of British Columbia. To reduce bias as much as humanly possible, it made Therapeutics Initiative wholly independent from the government, the pharmaceutical industry, and other vested interest groups. A telling statement on the website of Therapeutics Initiative sums up the group's mission: "We strongly believe in the need for independent assessments of evidence on drug therapy to balance the drug industry-sponsored information sources."⁴²

So it would be interesting to see what Therapeutics Initiative has to say about these statin trials, wouldn't it?

In Therapeutics Letter #48, an issue of its bimonthly letter series, the group tackled the question: "What is the overall health impact when statins are prescribed for primary prevention?" (Remember, primary prevention refers to the use of statin drugs to prevent a first heart attack or coronary "incident," whereas secondary prevention refers to the use of statin drugs to prevent a second heart attack.)

Interesting question, indeed. The scientists at Therapeutics Initiative analyzed five of the major statin trials—the PROSPER, ALLHAT-LLT, and ASCOT-LLA trials mentioned above, plus two published earlier.⁴³ Taken together, these five trials involved an overall population that was 84 percent primary prevention and 16 percent secondary prevention. In the pooled data, the statins reduced cardiovascular measures—total myocardial infarction (heart attack) and total stroke—by 1.4 percent. Yes, you read that right. Less than a 1.5 percent reduction in the very thing the drugs are supposed to prevent (heart attacks and strokes). "This value indicates that 71 mostly primary prevention patients would have to be treated for three to five years to prevent one such event," wrote the authors. (We wonder how many patients would eagerly sign on for statin therapy if they were asked the following question: Would you be willing to take an expensive drug that

has the possibility of serious side effects for three to five years in order to reduce your chances of a cardiovascular event by 1.4 percent?) Note that Therapeutics Initiative used the word “patients” in its analysis of the findings. Instead of the generic term “patients,” it should have used the more specific term “men.” Commenting on the evidence of benefit for primary prevention in women, the researchers reported that in women—28 percent of the total population of the studies—when coronary events were pooled, they were not reduced by statin therapy. “The coronary benefit in primary prevention trials appears to be limited to men,” they wrote.

Dietary factors and therapeutic lifestyle changes have no side effects. They should be considered the first line of defense in preventive cardiology.

And do we need to remind you that the stated benefit was a mere 1.4 percent reduction in heart attacks and strokes?

It gets worse.

“The other measure of overall impact—total mortality—is available in all five trials, and is not reduced by statin therapy.”

In other words, there was a small reduction in cardiovascular deaths but a corresponding increase in deaths from other causes, resulting in an overall mortality benefit of, let’s see, that would be . . . zero. And although the researchers clearly acknowledged that paltry less-than-2-percent reduction in heart attack and/or stroke, they also pointed out that this cardiovascular benefit was not reflected in two measures of overall health impact: total mortality (overall death rate) and total number of serious adverse events. “Statins have not been shown to provide an overall health benefit in primary prevention trials,” the researchers concluded.⁴⁴

A few years ago, John Abramson, M.D., author of *Overdosed America*, analyzed eight randomized trials that compared statin drugs with placebos. His findings and conclusions were published in a column in *The Lancet*,

and they echo the findings and recommendations of the researchers at Therapeutics Initiative. Here's what he wrote:

“Our analysis suggests that . . . statins should not be prescribed for true primary prevention in women of any age or for men older than 69 years. High-risk men age 30 to 69 years should be advised that about 50 patients need to be treated for five years to prevent one event. In our experience, many men presented with this evidence do not choose to take a statin, especially when informed of the potential benefits of lifestyle modification on cardiovascular risk and overall health. This approach, based on the best available evidence in the appropriate population, would lead to statins being used by a much smaller proportion of the overall population than recommended by any of the guidelines.”⁴⁵

Statins: A Final Cautionary Note

Millions of Americans will be taking statin drugs for decades, as recommended by the National Cholesterol Education Program's (NCEP) guidelines, and long-term side effects will become apparent, creating a whole host of pathologic situations. What does all this confusion and controversy mean to practicing physicians and the patients for whom they care? Dietary factors and therapeutic lifestyle changes have no side effects. They should be considered the first line of defense in preventive cardiology.

Look, there's not much doubt that statin therapy can significantly reduce the incidence of coronary morbidity and mortality for those who are at great risk of developing coronary artery disease.⁴⁶ But as research continues to implicate inflammation as the major coronary risk factor, cholesterol recommendations by groups such as the NCEP may need to be modified. Ultimately, hopefully, the attention paid to cholesterol will be proportional to its importance as a causative factor in heart disease, which is to say, not much.

Rather than selecting treatment options as a technician or a computer would do and targeting cholesterol numbers alone, doctors owe it to their patients—and patients owe it to themselves!—to look further into these controversial issues before embracing potent drugs that might not truly serve the needs of the people for whom they're being prescribed.

Although the use of statins in high-risk coronary patients—especially those with inflammatory markers—might be good medicine right now, overuse of these potent pharmacologic agents (that have both known and unknown side effects) for long-term use in otherwise healthy people is simply not justifiable.

CHAPTER 7

HELP YOUR HEART WITH THESE SUPPLEMENTS

ASK YOUR TYPICAL MAINSTREAM DOCTOR ABOUT NUTRITIONAL SUPPLEMENTS and the first thing you're likely to hear is this: "There's no good research showing they work." Both of us have heard this refrain time and time again when we discuss nutritional medicine with our more conservative colleagues.

It's not true.

You or your doctor can go online to the National Institute of Medicine's library (www.pubmed.com), enter into the search box the name of virtually any vitamin or herb you can think of, and, depending on what you choose, hundreds to thousands of citations will pop up. So the problem isn't an absence of research.

The problem is twofold. One, the conventional training of medical doctors in this country is highly biased toward pharmaceuticals. From the time they enter med school, doctors are courted by the pharmaceutical companies in myriad ways, some subtle, some not so subtle. Free lunches, symposiums, honorariums, consulting and lecturing contracts, vacations, perky pharmaceutical reps showing up at offices with the latest studies that show their products in a favorable light, free samples, and pens and prescription pads bearing the company's name—all create a culture in which pharmaceuticals are the first choice in any treatment plan. (Most docs will tell you these practices have no influence on them or what they choose to prescribe, but the research tells a very different story.¹)

The second part of the problem is that much of the research on vitamins flies beneath the radar. Your overworked doctor barely has time to scan the abstracts of the *New England Journal of Medicine* every month, let alone

dig deeply into the hundreds of studies that are published every year on vitamins and nutrients in journals like the *American Journal of Clinical Nutrition*. The vast majority of doctors in this country get no training whatsoever in nutrition, and those who do receive only the most rudimentary and superficial introduction to the subject. Put this together with the built-in medical school bias in favor of patent medicines, and it's easy to see why doctors often fail to think of natural substances as legitimate tools that can help keep people healthy.

Let's be clear. Conventional medicine is simply terrific at keeping people alive in emergencies. Both of us know that if we were to be in a car accident, we wouldn't want the ambulance rushing us to the nearest herbalist's office. We'd want to go to the emergency room of the best hospital we could find. But as good as conventional medicine is at treating people in acute situations, it's astonishingly bad at overall preventive care. It's great at keeping your heart beating if you've just had a heart attack. It's not nearly as good at keeping your heart healthy for the long run and keeping you, the heart's owner, out of the hospital in the first place.

The supplements listed in this chapter are some of the superstars for heart health that Dr. Sinatra uses in his practice (as he has for decades) and that Dr. Jonny has recommended to clients and written about extensively in his books and newsletters. Neither of us is saying you should just throw out your prescriptions and start randomly taking vitamins. But we *are* saying that natural substances such as vitamins, antioxidants, omega-3 fats, and many of the thousands of compounds found in foods may affect the health of the heart in an even more profound way than many of the medicines routinely prescribed as the first order of business.

Even if you're already on medication, nutritional supplements can still improve your health. In the case of coenzyme Q₁₀ (CoQ₁₀), for example, supplementation is an absolute must if you're on a statin drug (more on that in a moment). Magnesium is often used in conjunction with blood sugar drugs such as metformin (Glucophage) or blood pressure medications such as beta blockers. And virtually everyone needs a little help in reducing oxidation and inflammation, two of the most important drivers in the development of heart disease. Omega-3 fatty acids, for example, can be used by just about anyone, whether he or she is on medication or not (check

with your doctor for any possible contraindications, such as right before going into surgery).

The following list is far from exhaustive, but it will give you a good idea of how you can use supplements to keep your heart healthy, either alone or, in some cases, as an adjunct to conventional therapy.

COENZYME Q₁₀: THE SPARK OF LIFE

Coenzyme Q₁₀ is a vitamin-like substance found throughout the body and made in every cell. Among the many important things it does, CoQ₁₀ helps create energy from fuel (food) in the human body, just as a spark plug creates energy from fuel (gasoline) in a car.

A CoQ₁₀ deficiency affects your heart as profoundly as a calcium deficiency would affect your bones. We create less of it as we age, making it all the more important to supplement with CoQ₁₀ as we grow older.

Here's how it works: Your body uses a molecule called *adenosine triphosphate*, or ATP, as a source of energy (which is why ATP is nicknamed "the energy molecule"). Much like gasoline is the fuel that allows you to actually drive a car to any of a million destinations, ATP is the fuel that allows your body to perform any of a million activities, ranging from cellular metabolism to doing bench presses to dancing the tango. The body makes ATP by stripping electrons—tiny subatomic particles that carry a negative electrical charge—from food and then delivering those electrons to oxygen, which is an *electron receptor*. CoQ₁₀ is one of the carriers of these electrons, so it essentially helps the cells use oxygen and create more energy. Bottom line: CoQ₁₀ has the ability to increase the body's production of the energy molecule ATP, and this is a very good thing indeed.

Just as a gasoline engine can't work without spark plugs, the human body can't work without CoQ₁₀. It's an essential component of the *mitochondria*, which is command central for the production of cellular energy (ATP). Not coincidentally, the heart is one of the two organs where the most CoQ₁₀ is concentrated (the other being the liver). The heart never

sleeps, and it never takes a vacation. It beats more than one hundred thousand times a day, making it one of the most metabolically active tissues in the body, so it's very dependent on the energy-generating power of CoQ₁₀.

A CoQ₁₀ deficiency affects your heart as profoundly as a calcium deficiency would affect your bones. We create less of it as we age, making it all the more important to supplement with CoQ₁₀ as we grow older. (Although it's present in food, the only foods that have any CoQ₁₀ to speak of are organ meats such as heart and liver. It's also easily destroyed by too much heat or overcooking.)

As we've said, one of the biggest problems with statin drugs is that they significantly deplete CoQ₁₀ levels. You may recall from the previous chapter on statins that the same pathway that produces cholesterol (the mevalonate pathway) also produces CoQ₁₀, so when you block that pathway at its virtual starting gate (as statin drugs do), you not only reduce the body's ability to make cholesterol but you also interfere with its ability to make CoQ₁₀.

We've said this before, but in case you missed it the first time, it's important enough to repeat: If you are on a statin drug you must, repeat *must*, supplement with CoQ₁₀. We recommend at least 100 mg twice a day.

But CoQ₁₀ isn't just essential for those on statin drugs. We believe it's essential for everyone else as well, and *especially* for anyone at risk for heart disease.

CoQ₁₀ has been approved in Japan as a prescription drug for congestive heart failure since 1974. And even in the United States, the benefits of CoQ₁₀ for the heart have been well known since at least the mid-1980s. A study published in the *Proceedings of the National Academy of Sciences of the United States of America* in 1985 gave either CoQ₁₀ or a placebo to two groups of patients having class III or class IV cardiomyopathy according to the definitions put forth by the New York Heart Association (NYHA).² These are seriously ill folks. Class III patients have marked limitation in activity because of symptoms and can basically only be comfortable at rest or with minimal activity; class IV patients have severe limitations and

experience symptoms even while resting. (Most class IV patients are bedbound.)

So what happened when these very sick patients were given CoQ₁₀? Here's how the researchers themselves summarized the results: "These patients, steadily worsening and expected to die within two years under conventional therapy, generally showed an extraordinary clinical improvement, indicating that CoQ₁₀ therapy might extend the lives of such patients. This improvement could be due to correction of a myocardial deficiency of CoQ₁₀ and to enhanced synthesis of CoQ₁₀-requiring enzymes."³

Another study that lasted six years and was published in 1990 looked at 143 patients, 98 percent of whom were in the same two classes as the patients in the 1985 study.⁴ The participants were given 100 mg of CoQ₁₀ (orally), in addition to being treated in their conventional medical program. Eighty-five percent of the patients improved by one or two NYHA classes, and there was no positive evidence of toxicity or intolerance. "CoQ₁₀ is safe and effective long-term therapy for cardiomyopathy," the study authors concluded.

CoQ₁₀ also has the ability to reduce blood pressure. A recent meta-analysis of CoQ₁₀ in the treatment of high blood pressure reviewed twelve different clinical trials and found that across the board patients who received CoQ₁₀ supplementation had significant reductions in blood pressure compared to control subjects who didn't receive supplementation.⁵ It's no wonder that several studies have demonstrated a strong correlation between severity of heart disease and severity of CoQ₁₀ deficiency.⁶

You might recall that oxidative damage (oxidation) is one of the four major culprits in heart disease, and you might also remember that cholesterol in the body is never a problem until it becomes oxidized. It's only this oxidized cholesterol—specifically, pattern B LDL cholesterol—that is a problem, because pattern B LDL molecules are the ones that adhere to the cell walls and initiate or accelerate the process of inflammation. Why do we mention that here? Simple. CoQ₁₀ is a powerful antioxidant, inhibiting oxidative damage to LDL cholesterol and thus helping to prevent cholesterol from becoming a "problem" in the first place. It's far smarter to

prevent LDL from getting damaged and sticky in the first place than to use a sledgehammer pharmaceutical to reduce LDL as much as possible!

◀ WHAT YOU NEED TO KNOW

- Coenzyme Q₁₀ (CoQ₁₀) is a kind of “energy fuel” for the heart.
- Statins deplete CoQ₁₀; supplementation is an absolute necessity if you’re on a statin drug, and it is a very good idea even if you’re not.
- D-ribose is one of the components of the energy molecule ATP, which the body uses to power all activity.
- L-carnitine supplementation after a heart attack increases survival rate and makes it less likely you’ll suffer a second heart attack.
- Magnesium relaxes the artery walls, reduces blood pressure, and makes it easier for the heart to pump blood and for the blood to flow freely.
- Niacin will lower both triglycerides and the “bad” kind of LDL cholesterol. It also reduces a toxic substance called lipoprotein(a)—Lp(a) for short—and raises HDL. Don’t use the time-release kind.
- Omega-3s—especially from fish—lower the death rate from heart disease. They also lower triglycerides, resting heart rate, and blood pressure.
- Omega-3s are highly anti-inflammatory.
- At least twenty-eight clinical trials in humans show that pantothenic acid (vitamin B₅) produces positive changes in triglycerides and LDL cholesterol. It also increases HDL.
- Nattokinase and lumbrokinase are natural “clot busters.”
- Other supplements worth considering include vitamin C, curcumin, resveratrol, and cocoa flavanols.

Coenzyme Q₁₀ and vitamin E have a strange, almost symbiotic relationship. In rats given supplemental vitamin E, increases in blood levels of CoQ₁₀ were observed; in baboons given supplemental CoQ₁₀, the anti-inflammatory effects of vitamin E were increased; and in one study, CoQ₁₀ plus vitamin E actually lowered C-reactive protein (CRP), a systemic measure of inflammation. We think it's wise to make sure you're getting about 200 IUs or so of vitamin E a day (from mixed tocopherols with a high gamma vitamin E formula) in addition to your CoQ₁₀ supplement. (But read the section on vitamin E, "The Good, the Bad, and the Ugly," first!)

D-RIBOSE: THE MISSING LINK

D-ribose, a five-carbon sugar, is one of the components of ATP, the energy molecule the body uses to power all activities. Without D-ribose, there would be no ATP; without ATP, there would be no energy.

Both CoQ₁₀ and the nutritional supplement L-carnitine help facilitate the process by which the body manufactures ATP. Metaphorically speaking, they act like little elves, shuttling the material needed to make ATP to the factories where it's made, resulting in more efficient production of this important energy molecule. CoQ₁₀ and L-carnitine can be said to function like very efficient trucks transporting building materials to the factories where stuff actually gets built, but D-ribose is one of the actual building *materials*. A shortage of D-ribose means a shortage of ATP, and a shortage of ATP, especially in the heart, is bad news indeed.

D-ribose is synthesized in every cell in the body, but only slowly and to varying degrees depending on the tissue. Tissues such as the liver, adrenal cortex, and adipose tissue make plenty of D-ribose because they produce chemical compounds used to synthesize fatty acids and steroids, which are in turn used to make hormones.

But molecules of D-ribose made by these tissues are the opposite of rollover minutes on your cell phone—they have to be used right then and there and can't be “transferred” to other tissues that might need them, such as the heart. The heart, as well as the skeletal muscles and brain, can only make enough ribose for their day-to-day needs. They have no D-ribose saving account. When the cells of the heart, for example, encounter a stressor such as oxygen deprivation, they lack the metabolic machinery needed to quickly whip up some badly needed D-ribose ribose. Tissues that are stressed because they don't get enough blood flow or oxygen can't make enough D-ribose to replace lost energy quickly. And when oxygen or blood flow deficits are chronic—as in heart disease—tissues can never make enough D-ribose, and cellular energy levels are constantly depleted.

The D-ribose connection to cardiac function was first discovered by the physiologist Heinz-Gerd Zimmer at the University of Munich. In 1973, Zimmer reported that energy-starved hearts would recover much faster if D-ribose was given prior to or immediately following ischemia (an insufficient

supply of blood to the heart, usually as a result of blockage). Five years later, Zimmer demonstrated that the energy-draining effects of certain drugs used to make the heart beat stronger (called *inotropic agents*) could be significantly lessened if D-ribose was given along with the drugs.

The most important finding from Zimmer's research was that D-ribose plays an enormous part in both energy restoration and the return of normal diastolic cardiac function. (Diastolic *dys*function is basically a kind of heart failure.) One 1992 clinical study from Zimmer's group showed that administering D-ribose to patients with severe but stable coronary artery disease increased their ability to do exercise and delayed the onset of moderate angina (chest pain). Since then, the benefits of D-ribose have been reported for heart failure, cardiac surgery recovery, restoration of energy to stressed skeletal muscles, and control of free radical formation in tissues that have been deprived of oxygen.

Here's one dramatic story from Dr. Sinatra's practice that illustrates the almost miraculous power of D-ribose supplementation to improve the quality of life of cardiac patients:

Dr. Sinatra: The Case of Louis and D-Ribose

Louis came to my office suffering from severe coronary artery disease. He had been previously treated by having a stent placed in a major coronary artery, but he still had severe blockage in a small arterial branch that was difficult to dilate with a stent and next to impossible to bypass with surgery. He had what's called refractory angina, which means he experienced chest pain even with normal activities such as walking across a room. He'd also feel chest pain anytime he had even mild emotional stress. Louis had visited a number of cardiologists for his heart problem and had been placed on a number of common heart drugs, but his problems persisted.

When Louis came to my office I noticed high levels of uric acid in his blood, indicating faulty ATP metabolism. At the time, he was already taking L-carnitine and CoQ₁₀ at "maintenance doses." Realizing that it would help him enormously if he could build up his ATP stores, I immediately recommended D-ribose as well as increased doses of L-carnitine and CoQ₁₀. In just a few short days, Louis showed remarkable improvement. His son-in-law, a dentist, called me a few days later and reported, "You fixed Louis!"

An adequate dose of D-ribose usually results in symptom improvement very quickly, sometimes within days, as in Louis's case. If initial response is poor, the dose should be increased to 5 g (1 teaspoon) three times a day. Logically, those who are the sickest and the most energy depleted will notice the most improvement in the quickest time.

Despite accumulating scientific evidence of the benefit of D-ribose, very few physicians in the United States have even heard of it outside of their first-year med school biochemistry class. Fewer still recommend it to their patients. Those who are familiar with it have the wonderful gratification of seeing it help patients on a regular basis.

Although the optimal level of D-ribose supplementation will differ depending on the person and the particular condition, here are some good recommended starting points for supplementation:

- 5 g daily for cardiovascular prevention, for athletes on maintenance, and for healthy people who engage in strenuous activities or hard-core workouts
- 10 to 15 g daily for most patients with heart failure, ischemic cardiovascular disease, or peripheral vascular disease; for individuals recovering from heart attacks or heart surgery; for treatment of stable angina; and for athletes who engage in chronic bouts of high-intensity exercise
- 15 to 20 g daily for patients with advanced heart failure, dilated cardiomyopathy, or frequent angina; for individuals awaiting heart transplant; and for individuals with severe fibromyalgia, muscle cramps, or neuromuscular disease

Reported side effects are minimal and infrequent, and there are no known adverse drug or nutritional interactions associated with D-ribose use. The toxicology and safety of D-ribose have been exhaustively studied, and the supplement is 100 percent safe when taken as directed. (Thousands of patients have taken D-ribose at doses of up to 60 g a day with minimal, if any, side effects.)

However, even though there are no known contraindications for supplementation with D-ribose, we recommend that pregnant women, nursing mothers, and very young children refrain from taking D-ribose

simply because there is not enough research on using it in these populations.

L-CARNITINE: THE SHUTTLE BUS FOR FATTY ACIDS

As previously stated, the best way to conceptualize L-carnitine is to think of it as a transportation system. It acts as a kind of shuttle bus, loading up fatty acids and transporting them into tiny structures within each cell called *mitochondria*, where they can be burned for energy. Because the heart gets 60 percent of its energy from fat, it's very important that the body has enough L-carnitine to shuttle the fatty acids into the heart's muscle cells.

Studies of patients being treated for various forms of cardiovascular disease provide the strongest evidence for the benefit of L-carnitine supplementation. One study showed that people who took L-carnitine supplements after suffering heart attacks had significantly lower mortality rates compared to those of a control group (1.2 percent of the L-carnitine takers died versus 12.5 percent of the subjects in the control group).⁷ One randomized, placebo-controlled study divided eighty heart failure patients into two groups. One group received 2 g of L-carnitine a day, and the other group received a placebo. There was a significantly higher three-year survival rate in the group receiving L-carnitine.⁸

L-carnitine improves the ability of those with angina to exercise without chest pain.⁹ In one study, the walking capacity of patients with intermittent claudication—a painful cramping sensation in the muscles of the legs because of a decreased oxygen supply—improved significantly when they were given oral L-carnitine. In another study, patients with peripheral arterial disease of the legs were able to increase their walking distance by 98 meters when they supplemented with L-carnitine; they were able to walk almost twice as far as those who were given a placebo. Further, congestive heart failure patients have experienced an increase in exercise endurance on only 900 mg of L-carnitine a day.

And if that were not enough to establish L-carnitine's bonafides, it has been shown to be a powerful cardio-protective antioxidant. One paper published in the *International Journal of Cardiology* found that L-carnitine had a direct stimulatory effect on two important oxidative stress-related compounds (HO-1 and eNOS). Both of these markers have antioxidant, antiproliferative (meaning they have an inhibitory effect on tumor cells),

and anti-inflammatory properties, so ratcheting up their activity a notch is a very good thing indeed. The researchers concluded that this action of L-carnitine “would be expected to protect from oxidative stress related to cardiovascular and myocardial damage.”¹⁰

Dr. Sinatra: L-Carnitine and CoQ₁₀

Eighty-five percent of my patients with congestive heart failure have improved significantly on CoQ₁₀. But I was concerned about the 15 percent who, despite supplementation with CoQ₁₀, still had symptoms that severely compromised their quality of life.

These folks were supplementing with CoQ₁₀ and had excellent blood levels to show for it, typically 3.5 ug/mL or higher (the normal level of CoQ₁₀ is 0.5 to 1.5 ug/mL.) Nonetheless, these folks seemed to be unable to utilize what was in their own bodies.

As I read more about L-carnitine, I came to see that it might work in synergy with coenzyme Q₁₀, stoking the fire in the ATP production phase of the Krebs cycle (a sequence of reactions by which living cells generate energy). I finally got comfortable enough to recommend to some of my worrisome patients that they give it a try in combination with CoQ₁₀, and wow, what a difference!

These treatment-resistant folks came in with better color, breathed easier, and walked around the office with minimal difficulty. I was genuinely amazed. It was as if the L-carnitine provided a battery, working perfectly with the coenzyme Q₁₀.

The bottom line is that the heart is the most metabolically active tissue in the body, and thus it requires a huge and constant amount of energy molecules, or ATPs.

Remember, the heart has to pump sixty to one hundred times a minute, twenty-four hours a day, for years and years with no time off for good behavior! Cardiac muscle cells burn fats for fuel, so the heart is especially vulnerable to even subtle deficiencies in the factors contributing to ATP supply: coenzyme Q₁₀, D-ribose, and L-carnitine.

These nutrients make up three of what Dr. Sinatra calls the “Awesome Foursome” in metabolic cardiology. Now let’s introduce the fourth.

MAGNESIUM: THE GREAT RELAXER

Dr. Robert Atkins once referred to magnesium as a “natural calcium channel blocker,” and he was 100 percent correct. A few paragraphs from now, you’ll understand just why magnesium’s ability to block the channels by which calcium gets into the cells is so important for the health of your heart.

Recent research strongly suggests that calcium in the heart can be a huge problem. One meta-analysis examined fifteen eligible trials with the objective of investigating the relationship between calcium supplements and cardiovascular disease. The researchers concluded that calcium supplements (administered without vitamin D) were associated with a modest but significant *increase* in the risk of cardiovascular disease—an increase, they noted, that might well translate into “a large burden of disease in the population.” The authors called for a reassessment of the role of calcium supplements in the management of osteoporosis.¹¹

A second study had a different purpose, one particularly relevant to our story.¹² The researchers began with the premise that statins reduce cardiovascular risk and slow the progression of coronary artery calcium. The purpose of the study, then, was to determine whether lowering LDL cholesterol (as statins do) is in some way complementary to slowing the progression of coronary artery calcium. The researchers basically wanted to illuminate the relationship of these two phenomena as they relate to heart disease.

Here’s what they did. They measured the change in coronary artery calcium in 495 patients who were basically symptom-free at the beginning of the study. They did this by using a method known as electron beam tomography scanning. Right after their first scan, the patients were started on statin drugs, and they were followed for an average of 3.2 years, during which time their cholesterol was checked and they were scanned on a regular basis. Over the course of the 3.2-year follow-up period, 41 of the patients had heart attacks.

On average, the 454 patients who did *not* suffer heart attacks saw their arterial calcium go up by approximately 17 percent every year. But the 41 patients who *did* experience heart attacks saw a whopping 42 percent

increase per year in their arterial calcium. According to the researchers, having a faster progression of coronary artery calcium gives you an astonishing 17.2-fold increase in your heart attack risk.¹³

And get this: LDL cholesterol did *not* differ between the two groups. Ironically, the LDL levels of the folks who did *not* suffer heart attacks were slightly *higher* (though not significantly so) than the average LDL levels of the folks who *did* suffer heart attacks.

So let's summarize the results. Both groups—the 41 folks who *had* heart attacks and the 454 folks who didn't—essentially had the *same* LDL levels. (So if you were using patients' LDL levels to predict heart attacks, you'd get no better accuracy than you would by reading their horoscopes!) But if instead of LDL levels you looked at the levels of calcium in the arteries, it would be a whole different story. Those who suffered myocardial infarctions were the *most* likely to have higher calcium levels in their arteries, especially when the arteries became totally blocked.

Coronary artery calcification has long been recognized as a big risk factor for heart disease, but for some reason we continue to obsessively focus on cholesterol, while few people have heard much about the calcium connection.

Arthur Agatston, M.D., a Florida cardiologist best known as the author of *The South Beach Diet*, actually invented a scoring method to determine the severity of calcification in the arteries—it's known as the Agatston score. (Research shows that people with Agatston scores higher than 400 are at a significantly increased risk for coronary “events”—myocardial infarctions—as well as for most coronary artery procedures [bypasses, angioplasty, etc.].¹⁴)

Calcium in the bones? Very good. Calcium in the arteries? Not so good. Enter magnesium.

Magnesium and calcium have an interesting, symbiotic relationship. When magnesium is depleted, intracellular calcium rises. Magnesium also inhibits platelet aggregation, an important step in the development of clots. Calcium channel blockers widen and relax the blood vessels by affecting the muscle cells found in the arterial walls, which is exactly what magnesium does—splendidly, we might add. Magnesium dilates the

arteries, thus reducing blood pressure and making it far easier for the heart to pump blood and for the blood to flow freely.

In most of the epidemiologic and clinical trials, a high dietary intake of magnesium (at least 500 to 1,000 mg a day) resulted in reduced blood pressure.¹⁵ These studies showed an inverse relationship between magnesium intake and blood pressure; people who consumed *more* magnesium had *lower* blood pressure. One study of 60 hypertensive subjects who were given magnesium supplementation showed a significant reduction in blood pressure over an eight-week period.¹⁶

So basically, you can think of magnesium as a “relaxer.” One of the most relaxing things you can do is to bathe in Epsom salts, which is basically a compound of magnesium with a little bit of sulfur and oxygen. If you’ve ever worked with an integrative medicine practitioner who happens to use vitamin drips, you might have found that the most amazing and restful sleep you’ve ever had occurred after getting a magnesium-heavy vitamin push.* Just as magnesium has a relaxing effect on your body, it also has a relaxing effect on your arteries. And that’s a very good thing from the perspective of the heart, which instead of having to push blood through a narrow or constricted vessel (dangerously raising blood pressure) now has the much easier task of pumping it through a relaxed, widened vessel that doesn’t put up so much resistance. Your heart doesn’t have to work as hard, your blood pressure goes down, and all is well with the world.

There’s another interesting connection between magnesium and the heart, and if you’ve followed our argument so far, you’ll love the elegance of how it all comes full circle. The connection? Sugar.

You’ll recall from [chapter 4](#) that sugar is one of the worst things you can eat if you want to have a healthy heart. (To save you the trouble of looking it up, here’s why: Sugar is highly inflammatory. It also creates dangerous compounds known as advanced glycation end products, or AGEs, which play a pivotal role in atherosclerosis.¹⁷) AGEs play a role of particular importance in type 2 diabetes, which, as you know, is a condition in which blood sugar and insulin are essentially at unhealthy levels and have to be brought under control. (And diabetes is one way to fast-track your path to heart disease.)

One of the very best things magnesium does is help manage blood sugar. In several studies of diabetic patients, magnesium supplements of 400 to 1,000 mg per day, given for anywhere from three weeks to three months, improved a number of measures of glycemic (blood sugar) control, including the requirement for insulin.¹⁸ One study measured serum concentrations of magnesium in 192 people with insulin resistance and found that the prevalence of a low magnesium level was about 65 percent among those with insulin resistance, as opposed to only 5 percent of those in a control group.¹⁹

Clearly, there's a strong association between magnesium deficiency and insulin resistance. You'll recall that people with insulin resistance are at great risk for diabetes, which in turn puts them at great risk for heart disease. Helping to control blood sugar and insulin is just one more important way in which magnesium is critical for heart health.

Magnesium is necessary for more than three hundred biochemical reactions in the body, and many of these are enzymatic reactions, essential for heart health (or what scientists call *myocardial metabolism*).²⁰ Even borderline deficiencies of magnesium can negatively affect the heart, and not surprisingly, there is a considerable amount of evidence associating low levels of magnesium with cardiovascular disease.²¹

Bottom line: Magnesium supplements are a must for those who want to protect their hearts. Magnesium lowers blood pressure, helps control blood sugar, and relaxes the lining of the blood vessels. And almost all dietary surveys show that Americans aren't getting nearly enough.²² We recommend supplementing with at least 400 mg per day.

NOTE: Magnesium supplementation is *not* recommended for anyone with renal insufficiency (kidney disease).

NIACIN AND ITS EFFECT ON CHOLESTEROL

Even if your doctor hasn't studied nutrition and is skeptical (or worse) when it comes to supplements, chances are he or she will be familiar with the benefits of niacin. It's been known since 1955 that cholesterol can be effectively lowered with doses of 1,000 to 4,000 mg of niacin daily.²³ Subsequent studies have shown that niacin will lower triglycerides by 20 to 50 percent and LDL cholesterol by 10 to 25 percent.²⁴

Niacin is one of two major forms of vitamin B₃—the other is nicotinamide. Although both forms can be used for different things in the body, only the niacin form has an effect on your cholesterol, triglycerides, and related compounds. And the effect is not just on overall cholesterol. Studies have shown that when LDL cholesterol is reduced with niacin, there is a preferential reduction of the really nasty LDL molecules, the hard, small, BB gun pellet-type particles that stick to the artery walls, get oxidized, and cause damage.

Niacin also reduces lipoprotein(a), or Lp(a). Lipoprotein(a) is basically a special kind of LDL, and it's a really bad one. This, folks, is the *real* cholesterol story! Lp(a) is an independent risk factor for heart disease and for heart attacks, yet it doesn't get as much attention as cholesterol does because there aren't effective drug treatments for lowering it, and no one really knows what to do about it. Niacin lowers Lp(a) levels by a remarkable 10 to 30 percent.²⁵

Equally terrific, if not more so, is the fact that niacin *raises* HDL cholesterol. That alone would be worth shouting from the rooftops, because we consider HDL cholesterol to be a much undervalued player in the heart disease story. (We'll delve into this topic later on in the book.) Niacin raises HDL levels by 10 to 30 percent.²⁶ But even better is the fact that it *preferentially* increases HDL-2, which is the most beneficial of the HDL subclasses.²⁷ (HDL-3 is actually pro-inflammatory, even though it's a member of the so-called "good" cholesterol family—HDL—once again demonstrating how obsolete and ridiculous the classification of cholesterol into just "good" and "bad" really is!)

The most clinically important side effect of too much niacin is that it can be very taxing on the liver (a condition known as hepatotoxicity), although as Dr. Alan Gaby points out in his exhaustive review of nutritional supplements and disease, this is almost never seen in patients taking 3 g or less per day.²⁸

Abram Hoffer, M.D., the great pioneer of nutritional and integrative medicine, stated that his thirty years of experience with niacin therapy (usually 3 g a day or more) showed that one out of every two thousand patients will develop hepatitis from large doses of this vitamin. However, Hoffer also pointed out that in all of his patients who developed hepatotoxicity, liver function returned to normal after treatment was discontinued.²⁹

Sustained-release niacin is actually more hepatotoxic than regular niacin, and liver problems may occur at lower doses.³⁰ Nausea may be an early warning sign of niacin-induced hepatotoxicity; if nausea occurs, the dose should be reduced, or treatment should be stopped.³¹ For folks taking therapeutic doses of niacin, it's a good idea to have your doctor check your liver enzymes periodically using a standard liver function test.

Dr. Jonny: Niacin Flush

The first time I experienced the “niacin flush” I was working as a personal trainer. It was five o'clock in the morning, and I was getting ready for my six a.m. client. I remember drinking my protein shake, swallowing my vitamins, and then, a very short time later while getting dressed, having the distinct feeling that I was going to die. My skin was flushed, warm to the touch, and my cheeks (and arms) were pinkish red. It wasn't painful, but it was deeply unpleasant.

My six a.m. client happened to be the president of a high-end makeup company whose husband was an equally well-known Manhattan dermatologist (as well as the only doctor I knew who was likely to be awake at this ungodly hour). I called my client, and she immediately put her husband on the line. I described my symptoms, and he asked me if I'd taken or eaten anything unusual. “Just my vitamins,” I said, to which he replied without hesitation, “Oh, it's just the niacin. Nothing to worry about, it'll pass in a few. I'm going back to bed now.”

So that was my first encounter with the infamous “niacin flush.” It’s basically a temporary flushing of the skin, not at all dangerous (especially if you know it’s coming!), and it’s actually a result of the dilation of the blood vessels in the skin (which is why my skin turned pink). Some people experience itching as well or even a mild burning sensation. It typically goes away within a couple of weeks and can usually be counteracted with a baby aspirin taken beforehand.

NOTE: If you are diabetic or have a liver ailment, be sure to check with your doctor before supplementing with niacin.

Dr. Sinatra’s Niacin Know-How

- Look for straight, non-time-release niacin (also known as nicotinic acid). Take after meals at dosages of 500 mg to 3 g daily (see below).
- Start slowly at 100 mg. Work your way up gradually to a higher level, in divided doses.
- If the flush is too uncomfortable, take a baby aspirin before the first meal of the day and then take the niacin after the meal. Use the aspirin only as long as you experience the flush and whenever you increase your niacin dosage, which will trigger a flush.
- You can also try taking an apple pectin supplement with the niacin to reduce a flush.
- Niacin may increase the enzyme levels in liver function tests. This does not necessarily mean that niacin is causing a liver problem, but have your doctor keep an eye on it. He or she may suggest stopping the niacin for five days before your next liver test to avoid possible confusion. Be aware, though, that when you resume the niacin you will develop a flush.

VITAMIN E: THE GOOD, THE BAD, AND THE UGLY

For decades, the nutritional world revered vitamin E as something of a heart savior, a major antioxidant that defended against lipid peroxidation, which was thought to be the cause of cardiovascular disease. (*Lipid* simply means fat, and *peroxidation* is a fancy way of saying oxidative damage from free radicals.) During the 1990s the adulation for vitamin E even extended to mainstream medicine, going as far as the American Heart Association. In 1996, for instance, vitamin E was celebrated in a well-publicized study for significantly reducing cardiovascular events over the course of one year among some 2,000 patients with documented heart disease.

The successes and reputation of vitamin E prompted many to believe that if a little vitamin E was good, then more would be even better! Critical studies that followed, however, began demonstrating that daily doses of vitamin E at 400 IUs and above didn't necessarily generate beneficial results, and, in fact, might be detrimental to health. (As early as 2003, Dr. Sinatra wrote in his newsletter about his own reluctance to back high-dose vitamin E because the emerging research indicated possible pro-oxidant effects.)

That said, both of us found ourselves puzzled by the negative study results that have popped up since then. Sure, problems could come from using the synthetic form of vitamin E (designated *dl-alpha-tocopherol*) instead of the "natural" form (designated *d-alpha-tocopherol*). But a pro-oxidant effect from natural vitamin E, considered one of the powerhouses in the anti-oxidant armamentarium? How could that be?

Sharp-eyed readers may have noticed that we put quotation marks around the word *natural* when referring to natural vitamin E in the above paragraph. That's because d-alpha-tocopherol by itself is only one *part* of natural vitamin E. Vitamin E is actually a collection of eight related compounds that are divided into two classes: *tocopherols* and *tocotrienols*. The tocopherols come in four forms: *alpha*, *delta*, *beta*, and *gamma*. Of these four forms, the best known is alpha. When you purchase a "natural" vitamin E supplement, most of the time it is 100 percent *alpha-tocopherol*.

And therein lies the problem.

Gamma-tocopherol is turning out to be the most potent of the four tocopherols, and the one most responsible for vitamin E's positive effects as an anti-oxidant. Thus, people taking high-dose alpha-tocopherol alone and not getting enough gamma-tocopherol in their diets, or in their supplements, could run the risk of experiencing a pro-oxidant effect from vitamin E. Moreover, large doses of alpha-tocopherol could also deplete the body's existing gamma-tocopherol stores.

A 2011 study provided an even sharper image of the two faces of vitamin E. In laboratory experiments, researchers in Belfast found that vitamin E (alpha-and gamma-tocopherol) protects very low-density lipoprotein (VLDL) and LDL cholesterol against oxidation. That's a good thing! Yet they found a "surprising" pro-oxidant effect on HDL (high-density lipoprotein), the cholesterol particle that acts like a garbage truck, picking up harmful oxidized LDL and transporting it back to the liver for removal. Anything that can hinder HDL is of real concern.

Worth noting is that the researchers referenced a previous study in which taking a small amount of vitamin C along with your alpha-tocopherol helped *prevent* the negative, pro-oxidant effect of vitamin E on HDL. That wouldn't be the first time one nutrient helped another one out. We already know that CoQ₁₀ helps protect vitamin E in the body and gives it a hand by recycling it back to an active form after it's been oxidized in biochemical reactions. (We are big fans of the synergistic effects of nutrients.)

The other half of the vitamin E story concerns the four components known as the *tocotrienols*. Tocotrienols are turning out to be the real heavy lifters in the vitamin E family, at least when it comes to benefits for the heart. They have more potent antioxidant activity than tocopherols do.³² They also increase the number of LDL receptors, which helps with LDL removal.³³ Tocotrienols provide significant lipid-lowering effects in experimental animals, and most prospective studies have demonstrated the same thing in humans.³⁴

If you take vitamin E, we recommend that you always get it from a supplement labeled "mixed tocopherols" in order to avoid the problems that can occur with pure alpha-tocopherol supplementation. A vitamin E supplement that is 100 percent alpha-tocopherol is less effective and may even be problematic in high doses. Virtually all the studies showing

negative results used the alpha-tocopherol form or, worse, the synthetic dl-alpha-tocopherol form. (The dl-alpha-tocopherol form should be left on the shelf to rot!)

If you add 200 IUs of mixed tocopherols or high-gamma vitamin E to a regimen that also includes vitamin C and CoQ₁₀, you should be fine!

FISH OIL'S OMEGA-3: THE ULTIMATE WELLNESS MOLECULE

If you've read this book sequentially, you're already familiar with omega-3 fatty acids from our extensive discussion of them in [chapter 5](#), so here we'll highlight just a few of the many studies demonstrating the value of omega-3 fats for the heart. (We should also point out that there is equally compelling research documenting the positive effect of omega-3s on the brain as well,³⁵ but because this is a book on cholesterol and cardiovascular disease, we'll focus on the heart.)

More than thirty years ago, scientists began to notice very low rates of cardiovascular disease among Greenland Eskimos compared to age- and sex-matched Danish control subjects. Shortly afterward, they were able to link these low rates of heart disease to high consumption of omega-3s in the Greenland diet.³⁶ This discovery triggered an enormous amount of research on the role of fish oil in preventing heart disease. (On the day of writing this—December 7, 2011—a National Library of Medicine search for the term “omega-3 fatty acids cardiovascular” produced 2,524 citations.)

One recent review of omega-3s and cardiovascular disease by Dariush Mozaffarian, M.D., of the Harvard School of Public Health, concluded that omega-3 consumption “lowers plasma triglycerides, resting heart rate, and blood pressure and might also improve myocardial filling and efficiency, lower inflammation, and improve vascular function.”³⁷ Mozaffarian also noted that the benefits of omega-3s seem most consistent for coronary heart disease mortality and sudden cardiac death.

In case your eyes were beginning to glaze over from all the medical journal speak, let's sum it up in plain English: *There is reliable and consistent research evidence demonstrating that omega-3 fats, mainly from fish, lower the death rate from heart disease and lower the risk of sudden cardiac death.* This is hardcore evidence that fish oil saves lives.

One of the landmark clinical studies of omega-3 supplementation in a high-risk population was published in 1999 and was known as the GISSI-Prevenzione trial.³⁸ More than 11,000 patients who had suffered a heart attack within the past three months were randomly assigned to receive

either 1 g a day of omega-3s, 300 mg of vitamin E, both, or neither, in addition to whatever standard therapy they were receiving. Vitamin E had no effect, but omega-3s were associated with a 20 percent reduction in mortality and a whopping 45 percent reduction in the risk of sudden death. These effects were apparent within a mere three months of therapy.³⁹

International guidelines recommend 1 g of omega-3 fats daily for all people who've already had a heart attack or for patients with elevated triglycerides.⁴⁰ Experts believe these guidelines will soon be extended to patients with heart failure as well.⁴¹

It's worth mentioning that the overwhelming majority of research on omega-3s and heart disease was done using the two omega-3s that are found in fish, EPA and DHA. But other studies have also found that ALA—the omega-3 found in plant foods such as flax and flaxseed oil—has benefits for the heart as well. One review of the literature pointed out that both *in vitro* (test-tube) studies and animal studies have shown that ALA can prevent ventricular fibrillation, the chief mechanism of cardiac death, and that it might be even more efficient at preventing this than EPA and DHA are. The review also noted that ALA was effective at lowering platelet aggregation, which is an important step in thrombosis (a stroke or nonfatal heart attack).⁴²

Even if you're already on a statin drug and have decided to remain on one, fish oil can still help you. One study found that among more than 3,600 people with a history of cardiovascular disease—many of whom were on antiplatelet drugs, antihypertensive agents, and nitrates—daily fish oil supplementation led to a statistically significant 19 percent reduction in major coronary events compared to the control group.⁴³

Omega-3 fats, particularly from healthy, wild fish, are your heart's best friend, whether you're recovering from a heart attack or hoping to prevent one. They lower triglycerides. And they lower blood pressure. And best of all, omega-3s are among the most anti-inflammatory compounds on the planet, meaning they have a beneficial effect on the root causes of heart disease.

We recommend that you take 1 to 2 g of fish oil daily, and that you eat cold water fish (such as wild salmon) as often as you can. (We both recommend Vital Choice, an impeccable source of wild salmon from

pristine Alaskan waters that is reasonably priced and shipped in dry ice directly to your door.)

When you supplement with fish oil, remember that the total amount of omega-3s is not what's important. Bargain-basement omega-3 supplements often tout on their labels how much omega-3 they contain. This number by itself is meaningless. You want to know specifically how much EPA and DHA are contained within each capsule. These are the gold nuggets in the prospector's tin—you don't care about the *total* amount of stones in that pan, you care about the *gold*. EPA and DHA are the gold. Try to get at least 1 g daily of combined EPA and DHA. (For many of his patients, Dr. Sinatra prefers higher DHA, as it penetrates more into the heart, brain, and retina than EPA does, so he frequently uses squid or algae oil in addition to fish oil because of its higher DHA content.)

PANTETHINE: YOUR SECRET WEAPON

Pantethine is a metabolically active (and somewhat more expensive) form of vitamin B₅ (pantothenic acid). The blood tests of patients with dyslipidemia—a fancy way of saying that their blood levels of cholesterol are too high—significantly improve with pantethine supplementation. And although this can't be seen on a blood test, pantethine also reduces the oxidation of LDL.⁴⁴

No fewer than twenty-eight clinical trials in humans have shown that pantethine produces significant positive changes in triglycerides, LDL cholesterol, and VLDL, along with increases in HDL cholesterol.⁴⁵ In all of these trials, virtually no adverse effects were noted. The mean dose of pantethine in these studies was 900 mg per day given as 300 mg three times daily. This appears to be the optimal dosage, and it is the one we recommend.

According to a review of the literature on pantethine published in *Progress in Cardiovascular Diseases*, Mark Houston, M.D., noted that in most studies, at the end of four months pantethine reduced total cholesterol by 15.1 percent, LDL by 20.1 percent, and triglycerides by 32.9 percent, with an increase in HDL of 8.4 percent.⁴⁶ Houston also noted that in studies of longer duration, there appeared to be continued improvement. (The only adverse reactions were mild gastrointestinal side effects in less than 4 percent of the subjects.) As previously stated, we recommend 900 mg of pantethine divided into three daily doses of 300 mg each.

OTHER SUPPLEMENTATION YOU SHOULD CONSIDER

Picking the “top” supplements for treating any health issue is always difficult. In trying to keep the list from being too overwhelming, you’re always going to leave a few good things out. There’s also the very real issue of compliance. Most people don’t like to take a lot of pills, even if the pills in question are natural substances that will boost or protect their health. We consider the following supplements important, and we suggest that you read about what they do and consider using them in addition to the key supplements discussed above.

Vitamin C. Vitamin C is one of the most powerful antioxidants in the world, and because heart disease is initiated by oxidative damage (damage caused by free radicals), any help you can get in the antioxidant department is a good thing. And the evidence is not just theoretical: A large 2011 study published in the *American Heart Journal* found that the lower the level of vitamin C in the blood, the higher the risk for heart failure.⁴⁷ Take 1,000 to 2,000 mg a day.

Worth knowing: Vitamin C is extremely safe, and side effects are rare because the body can’t store the vitamin. (In some cases, doses exceeding 2,000 mg a day can lead to a little harmless stomach upset and diarrhea.) The bigger danger is the fact that vitamin C increases the amount of iron absorbed from foods. People with hemochromatosis, an inherited condition in which too much iron builds up in the bloodstream, should not take more than 100 mg of supplemental vitamin C.

Curcumin. This extract from the Indian spice turmeric has multiple benefits, not the least of which is that it’s highly anti-inflammatory. Scientific research has demonstrated its anti-inflammatory, antioxidant, anti-thrombotic, and cardiovascular protective effects.⁴⁸ Curcumin also reduces oxidized LDL cholesterol.⁴⁹ In animal studies, it was shown to protect the lining of the artery walls from damage caused by homocysteine.⁵⁰ The synergistic relationship of curcumin with resveratrol is especially important.

Resveratrol. Resveratrol is the ingredient in red wine that's best known for its "anti-aging" activity. It helps protect the arteries by improving their elasticity, inhibits blood clots, and lowers both oxidized LDL and blood pressure.⁵² Not a bad résumé! It's both a strong antioxidant and a strong anti-inflammatory, inhibiting a number of inflammatory enzymes that can contribute to heart disease. It also inhibits the ability of certain molecules to stick to the arterial walls, where they can take up residence and contribute to inflammation.⁵³ The recommended daily dose is 30 to 200 mg of trans-resveratrol, the active component of resveratrol. Read labels carefully to see what percentage of the capsule is actually the "trans" variety, because that's the only kind you care about.

NATURAL CLOT BUSTERS: NATTOKINASE AND LUMBROKINASE

Hyperviscosity refers to sticky, or sludgy, blood. When blood thickens, it bogs down as it moves through the blood vessels, causing platelets to stick together and clump. Blood vessels become more rigid, less elastic, and frequently calcified. The danger lies in the tendency to form clots that can block vessels leading to vital organs.

Nattokinase is extracted from the traditional fermented soy food natto, believed by many researchers to contribute to the low incidence of coronary heart disease in Japan. It provides a unique, powerful, and safe way to eliminate clots, or reduce the tendency to form clots, and thus decrease the risk of heart attack and stroke.⁵¹

Lumbrokinase, developed in both Japan and China, comes from an extract of earthworm, a traditional source of healing in Asian medicine. These two separate products of dynamic Asian research share a powerful and common property of great interest to anyone who wants to protect their cardiovascular system: They are natural clot eaters.

Here's how it works: Your body naturally produces *fibrin*, a fibrous protein formed from fibrinogen. (A fibrinogen test is one of the blood tests we recommend—see [chapter 9](#)—because it is a good marker of how much fibrin you're making.) Fibrin is both good and bad. Its clot-forming action is immediately activated when bleeding occurs, so that's a good thing. But excess fibrin activity can produce consistently thick blood, and that's a big problem.

To offset the danger—and to create thinner blood—the body produces another substance called *plasmin*, an enzyme whose job is to break down excess fibrin. A nice system of checks and balances. But if plasmin, the natural anticlotting agent, becomes overwhelmed and can't keep up with the job, there's trouble in River City. And that's where nattokinase and lumbrokinase come in. If blood clots in an already narrowed blood vessel, you're basically screwed. So if you can dissolve the clotted material, you can open arteries and improve blood flow. If you reduce the clot even just a tiny bit, you get a significant blood flow boost.

Nattokinase and lumbrokinase are natural blood thinners. They can literally turn your blood from the consistency of ketchup to the consistency of red wine! Best of all, they work pretty quickly, within minutes to hours.

If you take these supplements preventively, you may not form clots in the first place.

Cocoa flavanols. Plant chemicals in cocoa known as *flavanols* help the body synthesize a compound called nitric oxide, which is critical for healthy blood flow and healthy blood pressure. Nitric oxide also improves platelet function, meaning it makes your blood less sticky. It also makes the lining of the arteries less attractive for white blood cells to attach to and stick around. Researchers in Germany followed more than 19,000 people for a minimum of ten years and found that those who ate the most flavanol-rich dark chocolate had lower blood pressure and a 39 percent lower risk of having a heart attack or stroke compared to those who ate almost no chocolate.⁵⁴

Cocoa flavanols now come in supplement form, so if you prefer not to eat a couple squares of dark chocolate a day, consider a supplement.

CONVINCING YOUR DOCTOR

If you show this chapter to your doctor, and he or she is still skeptical, we suggest you direct him or her to the superb review paper on nonpharmacological treatment for dyslipidemia written by Mark Houston, M.D., and published in *Progress in Cardiovascular Diseases*.⁵⁵ This paper has 421 citations and should go a long way toward reassuring him or her that there is plenty of research to support the use of these natural, non-toxic substances.

CHAPTER 8

STRESS: THE SILENT KILLER

IF YOU LIKE DETECTIVE STORIES, YOU'RE GOING TO LOVE THIS.

Back around 2000, a story came out about how the population of gray tree frogs in many American lakes was being decimated. The general consensus was that this was due to the use of a common pesticide, carbaryl (known by the brand name Sevin), which was found in large quantities in all of the lakes where frogs were dying. Carbaryl was clearly the villain, and environmentalists demanded that the company making carbaryl be held accountable.

A familiar story, right?

But here's the thing: The manufacturers insisted that carbaryl wasn't harming the frogs. They had a ton of studies showing that if you took the little creatures out of their lake homes, put them in a lab, and exposed them to the pesticide, nothing happened to them.

But the tree frogs were still dying. And the environmentalists were positive it had something to do with their continued exposure to this pesticide.

So who was right?

As it turns out, they both were. The studies were accurate. Self-serving though it might have been, the big, bad industrial manufacturer had good science showing that frogs were not being knocked off by its chemical. And the environmentalists had *equally* good science showing that carbaryl was the likely suspect in this massive decimation of gray tree frogs, frogs that managed to survive just fine, thank you very much, as long as there wasn't any carbaryl around.

Enter Columbo in the form of Rick Relyea, Ph.D., a biochemical researcher from the University of Pittsburgh. Long story short, here's what he discovered: The pesticide, carbaryl, was indeed pretty innocuous to frogs (meaning it didn't kill them, at least) in the unnaturally tranquil setting of a lab. But most tree frogs don't live in a lab; they live in the wild, where there are constant dangers from predators. When the frogs pick up a predator signal, when they literally "smell danger," they secrete powerful stress hormones, just like our ancestors did when running from a wildebeest, or like we do when we're caught in traffic or miss a deadline. Expose a *stressed* frog to the pesticide, and you've got a dead frog. Neither stress hormones nor pesticides alone were enough to kill the average tree frog, but the *combination* of the two—stress hormones and pesticides—was lethal.¹

Subsequent studies over the next decade looked at the interaction between these two stressors—chemicals and predators—and examined how they interacted in a number of different organisms, including salamanders.² Several of the studies tested different pesticide chemicals with and without "predator cues" (signals that trigger the release of stress hormones), and every study confirmed that the combination of a pesticide and predator cues was far more lethal than any of the chemicals alone.

The take-home point, and the reason for this story, is that environmental elements *interact* with physiological elements in ways that can cause serious problems. (In the case of the gray tree frog, the interaction was a death sentence.) Although certain environmental and physiological elements might not be detrimental by *themselves*, when they're combined they can sometimes spell big trouble.

And the element of our physiology that's most likely to cause major problems for the health of the heart happens, not coincidentally, to be the subject of this chapter: stress.

THE STRESS RESPONSE IN ACTION

Imagine, if you will, that you are a zebra grazing on the plains in the African Serengeti. Everything is peaceful, the grass is delicious, the sun is out, and all is well with the world. Suddenly you hear a faint rustling in the woods. You look up and see behind a bush the outline of a lion, a lion that is looking straight at you. You can almost see the thought bubble over its head: “Lunch!”

Your body switches into full alert, the equivalent of flipping to “red” in the Department of Homeland Security’s threat advisory system. The moment you see the lion, your hypothalamus, a section of the brain that acts as a kind of “first responder” in emergency situations, sends a hormonal signal to your pituitary gland. Instantly, the pituitary relays the message to the adrenal glands, two little walnut-shaped glands that sit on top of the kidneys. Their job is to pump out hormones whose actions are your only hope of living long enough to eat lunch tomorrow rather than becoming lunch today. These hormones—cortisol and adrenaline, specifically—are known as the stress hormones, and whether you’re a zebra running from a lion or a caveman running from a woolly mammoth, you have them to thank for your survival.

But these wonderfully adaptive, life-saving hormones have a dark side. They can, and do, contribute mightily to heart disease.

Let us explain.

Your stress hormones, also known as the “fight or flight” hormones, serve as a kind of turbocharger when you’re in a threatening situation. Without them, you’d be unable to react quickly enough to protect yourself from a predator or any other kind of danger. Cortisol and adrenaline, working together, and working far more quickly than you can read these words, prepare the body for action. Adrenaline, for example, immediately raises your heart rate and blood pressure as your heart begins to furiously pump blood through the vascular system in a mad rush to get it to the organs and muscles that need it most. Cortisol, the main stress hormone, causes sugar to be released into the bloodstream so that it can be delivered to the muscle cells and burned for energy, which happens to be particularly useful if you’re running for your life.

In response to these hormonal signals, the body diverts blood from wherever it's not needed and directs it to where it is needed. (After all, if you're running from a wild boar, it doesn't make much sense for your body to send a ton of blood to your fingers, ears, reproductive organs, or digestive system.) The whole system is exquisitely designed to deliver just the right amount of nutrients, oxygen, and blood to the places where it's most likely to contribute to your survival (the running muscles and the heart, for example).

This is the stress response in action. It's meant to be quick, instant, and effective, its purpose singular: keeping you alive in a life-and-death situation. In the case of the zebra, it lasts only as long as it takes to get away from the lion, after which the zebra's metabolism returns to normal, its heart rate slows down, and it goes back to grazing, blissfully forgetful that there was ever a problem in the first place.

Acute Versus Chronic Stress

This natural ability of animals to live in the moment as opposed to sitting around wondering whether there's going to be another lion behind the next bush is what the great neurobiologist Robert Sapolsky was referring to when he titled his masterpiece on stress physiology *Why Zebras Don't Get Ulcers*.

Sapolsky's zebras experienced *acute* stress, which is ultimately temporary (unless of course the zebra is a slow runner, in which case the point is moot). Acute stress passes quickly, allowing us to return to "normal" and go about our business. The far more dangerous kind of stress, the kind that directly affects heart disease, is *chronic* stress. And that's a whole different animal.

So here's the big difference between the *acute* stress experienced by the zebra and the *chronic* stress that damages your heart. Acute stress is immediate and attention-grabbing. Your brain registers the threat of the marauding lion, and your stress response is instantly activated. It's energetic, it's explosive, and it's wonderful—it's what saves your life in an emergency. But if you turn it on too often, too long, or for psychological reasons—essentially the definition of chronic stress—you set yourself up for getting sick.

When stress persists, as it often does in people today, especially in those with certain personality and character traits, the abundance of cortisol from the adrenal cortex begins to promote hardening of the arteries.

Hypervigilance, or being constantly on guard (that sense of waiting for the other shoe to drop), may also create an overabundance of cortisol, thus turning a *psychological* coronary risk factor into a *physical* one. With this kind of chronic stress, we can overdose on our own adrenal hormones, making the heart vulnerable to unexpected cardiac events, such as heart attacks or arrhythmias. Remember that this damage doesn't always occur immediately, but it will occur when the adrenal glands are pushed to the point of exhaustion. Overwork, prolonged stress, and exhaustion—all of which contribute to burnout—are harbingers of death by hormonal overdose. More on this in a moment.

The common notion that stress is just a psychological state—that it's “all in your head”—is as outdated as the notion that cholesterol causes heart disease.

Stress, Stress, Who's Got Stress?

If we asked you right now to sit down and list the top ten things in your life that you find stressful, we bet that none of you would have the slightest problem coming up with a list. (In fact, the challenge would be limiting it to only ten items!) We further bet that your list would be front-loaded with psychological stressors—deadlines, traffic jams, sick kids, money, relationships—all of which take a constant toll, physically and psychologically.

But the common notion that stress is just a psychological state—that it's “all in your head”—is as outdated as the notion that cholesterol causes heart disease. Stress has physical and physiological correlates. When you're under stress, your body releases specific hormones that have specific actions and measurable results.

The stress response can save your life. It can also kill you.

The Roseto Effect

Once upon a time, a country doctor was at a little tavern in Pennsylvania when he walked a doc from the “big city”; he was the head of medicine at the University of Oklahoma. The two physicians started talking shop over a couple of beers, and the local doc happened to casually mention a puzzling observation: Folks in his town were dying from heart disease at half the rate of the rest of the country.

Although this might sound like it’s the opening scene for some kind of reverse horror story—instead of being struck by some weird, alien disease, towns-people seem to be mysteriously protected from the very diseases that kill their neighbors!—it’s actually a true story. The meeting took place in the 1960s; the town was Roseto, Pennsylvania; and that chance meeting between two doctors at a local bar eventually led to an influx of medical researchers trying to understand the strange phenomenon, a phenomenon that ultimately became known as the “Roseto Effect.” (Google it. Go on. We’ll wait.)

◀ WHAT YOU NEED TO KNOW

- Stress contributes to every disease known. And it can slow or prevent recovery.
- When you’re under stress, your adrenal glands produce stress hormones, known as “fight or flight” hormones. The main stress hormones are cortisol and adrenaline.
- An excess of stress hormones can create metabolic havoc and inflammation, and contribute to heart disease. When stress persists, the abundance of cortisol begins to promote hardening of the arteries.
- Stress causes the overproduction of platelets in the blood, which can then clump together and ultimately create a clot called a thrombus. When a thrombus blocks an artery to the heart, you have a heart attack.

In defiance of all logic, the residents of Roseto seemed to be eerily protected against heart disease. In Roseto the rate of death from heart disease was next to *zero* for men between the ages of fifty-five and sixty-four, not exactly an age group known to be immune to heart attacks. Men over the age of sixty-five did occasionally die from heart disease, but at a rate of about half the national average.

Okay, what could have been going on here? Tell the average American about the Roseto Effect, and he or she will probably say that the people of Roseto must have been living really healthy lives, going to the gym, eating low-fat diets, staying away from cholesterol, going easy on the salt, not eating red meat, and all that good stuff, right? That's got to be the answer.

Well, not exactly.

Roseto, Pennsylvania, was, to put it gently, a hardscrabble town. Life was anything but easy. The men spent their days doing backbreaking, hazardous labor in underground slate mines. Their traditional Italian food was Americanized in the worst possible ways. They fried everything in lard. Most, if not all, of the men smoked. If there was a contest for "most likely to die of heart disease," the men of Roseto could have won hands down.

So why weren't they dropping like flies?

That's exactly what the medical researchers wanted to know.

Here's what they found: Nearly all the houses in Roseto contained three generations of family members. Rosetans didn't put their elderly in assisted living homes; they incorporated them into community life. They treated them as wise village elders. Folks took evening strolls. They belonged to tons of social clubs. They participated in church and had community festivals. And remember those dinner tables piled high with the lard-fried food we mentioned a few paragraphs back? Those dinner tables happened to also offer enormous nourishment for, and nurturance of, the human spirit. They were family affairs where people connected, shared their experiences, and participated in family life in myriad ways.

Oh, by the way, the crime rate in Roseto—as well as the number of applications for public assistance—was zero.

What accounts for the Roseto Effect? Researchers now believe that the explanation can be summed up in two words: *community* and *connection*. These two things were (and are) such powerful protectors of health that

they were apparently able to offset both cigarette smoking and a horrific diet.

Writing about the Roseto Effect in their classic book, *The Power of Clan*, Stewart Wolf, M.D., and sociologist John Bruhn correctly observed that the characteristics of tight-knit communities such as Roseto are *far* better predictors of heart health than cholesterol levels or even smoking. The social structures of communities such as Roseto are characterized by predictability and stability, with each person in the community having a clearly defined role in the social scheme of things. Everyone worked in Roseto, and they worked hard, all for a shared communal goal: creating a better life for their children. Being connected to other people in a close community makes you far less likely to be overwhelmed by the problems of everyday life. Being less likely to be overwhelmed by the problems of everyday life means you're *also* less likely to be a victim of chronic stress.

And chronic stress is one of the biggest contributors to heart disease.

The men of Roseto had a ton of physical stressors in their lives. Working in the slate mines is hardly a day at the beach, and smoking certainly qualifies as a major physical stressor. But because the men were generally protected from the constant, unending mental stress that many folks endure on a daily basis—protected, presumably, by their close-knit community and their secure, nurturing family ties—these physical stressors didn't seem to produce the collateral damage such stressors might be expected to produce. The absence of chronic mental stress seemed to afford the men some level of protection against heart attacks.

To understand why, we have to understand something about the stress response in general. And the best place to start is with a man named Hans Selye.

THE “INVENTION” OF STRESS

Selye didn't invent stress, but he sure put it on the map. Back in the 1930s, Selye was a young researcher and assistant professor at McGill University in Montreal, and he was just beginning his work in the field of endocrinology—the study of hormones and what they do. A biochemist working just down the hall from Selye had isolated a specific substance from the ovaries, and everyone was wondering what the heck that ovarian extract actually *did*. So Selye did what any ambitious, unknown researcher would do—he got a bucketful of this strange ovarian stuff and decided to test it out on his rats.

Every day Selye would inject the rats with this mysterious stuff. But the thing is, Selye was a klutz. He'd try to inject the rats, but he'd drop them, or miss them, or they'd run behind the refrigerator. Selye wound up spending half the day running around the lab with a broom trying to coax the rats out from their hiding places and herd the terrified animals back into their cages.

After a few months passed, Selye began examining the rats to find out what the heck this stuff he'd been injecting them with did. Lo and behold, all of them had ulcers. Not only that, but they also had greatly enlarged adrenal glands and shrunken immune tissues. Selye was delighted. Clearly he'd discovered something important and new about the ovarian extract his colleague had discovered: It gave you ulcers!

Selye was at heart a good scientist, even if he had absolutely no talent for handling animals. And a good scientist always runs a control group, which is exactly what Selye did. The control group, of course, was a group of rats identical to the first group in every way except that they were *not* injected with the mysterious ovarian extract.

When Selye examined the rats in the control group, he made an even stranger discovery than before: All of the control rats *also* had ulcers.

Hmm.

Here he had two groups of genetically identical rats. One group had been injected with a substance, and the other had not, yet both groups wound up with ulcers. Thus, Selye quickly reasoned that the ovarian hormone couldn't have been causing the ulcers. What *else* did the two sets of rats have in common?

The answer wasn't hard to figure out, especially for a research-trained scientist such as Selye. The one thing both groups of rats had in common was Selye.

Selye had properly concluded that the ovarian hormone couldn't possibly be responsible for the ulcers and swollen adrenal glands, because both groups of rats had developed ulcers, and only one of them had been exposed to the hormone. But perhaps his own inept handling of the rats—the incompetent injections, the dropping, the chasing, the running around—had something to do with it. Selye reasoned that the ulcers—as well as the shrunk immune tissues and enlarged adrenals—were some kind of response to *general unpleasantness*, which he came to refer to as *stress*.

So Selye set out to test his new theory. He created a high-stress environment. He put some of the animals up on the roof during the winter months. He put others in the basement next to the boiler. Others underwent stressful surgeries, or were subjected to very loud music, or were deprived of sleep.

Every one of them got ulcers. Every one of them had swollen adrenals.

From this early work, Selye eventually developed what's known as the General Adaptation Syndrome (GAS) theory of stress. The theory holds that the effect of stress on the body develops over three stages: alarm, resistance, and exhaustion. Here's how it works.

The Three Stages of Stress

In the *alarm* stage, you recognize that there's a danger. Your body secretes a bunch of adrenaline and cortisol to prepare you for action (i.e., fight or flight). Of course, if all this available energy is *not* used for physical action, big problems develop. For example, too much adrenaline will raise your blood pressure and ultimately damage the blood vessels of the heart and brain.

Selye eventually developed what's known as the General Adaptation Syndrome (GAS) theory of stress. The theory holds that the effect of stress on the body develops over three stages: alarm, resistance, and exhaustion.

In the *resistance* stage, you deal with the stressor. If (hopefully) the situation resolves quickly, you return to something approaching a balanced state (what physiologists call *homeostasis*). Your stress hormones may come down, but you have also depleted some of your resources. More commonly, however, the situation persists, and now your body has to find a way to deal with it. Your body keeps trying to adapt and remains in a constant state of arousal. But you can't keep this up forever, with the stress pedal pressed to the metal and a ton of hormones pumping out into the bloodstream. If this continues too long, or if you repeat this process too often with too little recovery, you eventually move into the third stage.

This stage, aptly named the *exhaustion* stage, is also known as *burnout*. It's what we're referring to in this book when we talk about "maladaptation." Stress levels go up and stay up. These chronic stress levels deplete your immune system (one reason marathon runners are so much more susceptible to colds in the days following a race). Chronic stress levels also injure tissue cells, particularly in an area of the brain known as the *hippocampus*, which is involved with memory and cognition. (That's one reason you can't remember stuff you know when you're taking a very stressful exam.) Animal studies have demonstrated that the hippocampus actually shrinks under the weight of cortisol overload. And all of this has profound implications for high blood pressure and heart disease.

How You Cope with Stress Matters More Than the Stress Itself

So what's a stressor, anyway? It can be anything—and it's different for different people. Technically, a stressor is something to which special weight and significance has been attached. A stressor can be something as

simple as the feeling of being overwhelmed. It can be the inability to give in to a situation (resistance), a fear of losing control, or a feeling of struggle or uncertainty. Often a stressor can't be changed or even controlled—a hurricane or natural disaster, for example. What *can* be controlled, however, is your behavioral response to the external stressor. As Werner Erhard once said, “Riding a raft down white water rapids, a master has no more control over the water than you do. The difference is that a master is *in control* being *out of control* [Italics ours].”

Stressors come in all sizes, flavors, and packages. Hunger and deprivation are usually more significant stressors than a flat tire—except if you're a young woman who has to deal with a flat tire on a deserted country road late at night with no jack! A failing grade sounds like it would be a lot more important to a college student than, say, a bad haircut, unless perhaps the haircut damages an already low self-esteem. In these cases, the flat tire and the bad haircut can be considered strong external stressors in the person's life. How people respond to these (and other) stressors will determine their body's physiological reaction and, ultimately, their health.

When the promotion doesn't come, when the tire goes flat, when the haircut makes you look like Pee-wee Herman, you have only two choices—adapting or *not* adapting. You can adapt by “going with the flow,” accepting the situation, or working to effect some kind of change. Or you can *maladapt* by preparing your body for “combat,” either by withdrawing or pushing beyond normal expectations in an effort to make the stressor go away. When your coping styles are unhealthy and inappropriate—for example, abusing drugs or alcohol, overeating, or overworking—that's maladaptability. And these activities take an enormous toll on the body.

The big difference between stress in the caveman era and stress in the modern era is that the caveman's stress—and his adaptive responses—were largely physical. Ours are mental. We're not fighting off saber-toothed tigers, or running up trees to escape from bears, or in danger of being attacked by a neighboring tribe. Instead, we have to “fight back” mentally and keep “cool” at the same time, leaving the nervous system and the cardiovascular system in a state of constant and continuous “overpreparedness.” It's this continual state of visceral vascular readiness that makes the heart so darn vulnerable. The chronic alarm reaction that

develops is a harmful response in which the body continuously overdoses on its own biochemicals.

The biochemical alterations that occur in response to stress are powerful. When these responses are inappropriate or ineffective (e.g., screaming and pounding the wheel when you've been stuck for two hours in unmoving traffic on California's 405 freeway), you are *maladapting* rather than adapting, and pathological changes can (and do) occur in the body. The disruption in hormonal secretions can be long term and even permanent.

Much of the answer in dealing with stress lies not in the stressors themselves, but in the way we *deal* with the stressors (which, like in-laws and taxes, have an annoying tendency to not go away). An important first step is to recognize the situations that create stress for you. These frequently include lack of communication, unfulfilled expectations, retirement, death of a loved one, job pressures, bad relationships, and, particularly important, dwelling upon past events or imagined future ones.

Dr. Jonny: Is It the Stress or Is It the Response?

I grew up in a large, seven-room co-op in Jackson Heights, Queens (New York City). Many years ago, when my parents were in their late sixties, they went on a weeklong vacation to Bermuda. When they got back, the apartment was essentially empty.

Burglars had cased the joint and done a darn good job of it. No one saw or heard a thing, including their very friendly neighbors who would have called the police in a heartbeat had they suspected anything fishy was going on. The burglars clearly knew when people would be around and were exquisitely well prepared. They stripped the house as quickly and efficiently as a school of piranha might strip the meat from the carcass of a dead cow.

That house contained just about every material thing of any value that my parents had jointly collected over thirty-five years of marriage.

So that's what happened. A pretty big stressor, wouldn't you say?

My mother's response was one of her finer moments and one I will always remember.

"You know," she said, "the important things—our health, our family, our love—they didn't take. Sure, I'm sad to see all this stuff go. But you know what? It's kind of exciting in a way. Now we have the opportunity to create something completely new. We can design new rooms, get some new furniture, which I've been wanting to get anyway, and basically start again."

By shifting the way she reacted to this event, she turned it from a potential tragedy and enormous stressor into something that oddly enough sounded like an adventure.

What happened couldn't be changed. But how she reacted was in her control. Her reaction is what determined the toll this stressor would take

on her. It was her reaction—not the stressor itself—that determined the result.

And the result—thanks to her attitude and serenity—was that minimal damage was done to her health.

You can't control the “event” (i.e., what actually happens), but you can control the “story” (i.e., what you make it mean). By making this event mean opportunity rather than tragedy, my mother probably saved herself quite a lot of physical damage, and in the long run that probably extended her life.

STRESS AND YOUR HEART

When you're under constant (chronic) stress, you secrete *more* hormones, such as epinephrine and the glucocorticoids, which prepare the body to fight or flee. At the same time, you make *less* of other hormones, such as growth hormone. Why? Because at this point, at least from the body's point of view, these hormones are a big waste of time.

When your life is at stake, or your body *thinks* it is, your body does an instant evaluation (like a triage nurse) and decides what's essential and what's not. When you're running for your life, it doesn't make much sense to invest energy in reproductive or digestive functions, and it doesn't make sense to increase circulation to the stomach or the ears. What *does* make sense is keeping you alive, so the body diverts blood from the gut and sends it to the legs (so you can run faster). It doesn't bother with little extras, such as growth hormone or sex hormones, because if you're not going to be around past dinnertime, what's the point? Instead, it mobilizes all of its resources to combat the immediate life-threatening problem at hand.

This “triage” phenomenon was first noted around 1833 by a bunch of physician scientists treating a man with a gunshot wound.³ When the docs were about to patch him up, they noticed, not surprisingly, that he had a significant amount of red and rosy blood flow beneath where his guts were exposed. Then, for some reason—who knows, maybe he didn't like the doctors' aftershave—the guy got pissed off and angry. His body treated his anger and pissed-off-ness as an emergency, and his stress response kicked in immediately. Suddenly that red and rosy blood they were seeing in his guts turned pink and pale. It was almost as if all that deep red blood had disappeared!

So what happened?

What the docs were witnessing was a vivid visual example of the triage phenomenon described earlier. Stress hormones divert blood flow from the areas that aren't immediately necessary to your survival and send it to where it can do the most good in an emergency—the heart, lungs, and running muscles. That's why the blood in the guts of the guy with the gunshot wound changed color.

So your body perceives a life-threatening emergency (and remember, your body makes no distinction between an “old-school” emergency, such as an attacking lion, and the modern version of the same thing, such as being stuck for hours on the freeway). But releasing stress hormones that divert blood from nonessential to essential areas is only the beginning. You also need to get *more* blood into your system, or at least make sure you don’t lose any of the blood you already have! (Remember, from an evolutionary and historical point of view, most life-threatening “emergencies” carried with them the distinct possibility of blood loss!)

Now what does your body do? It makes more of a certain type of red blood cell called a *platelet*. Platelets stick together and form clots, which, when you think about it, is a pretty spiffy protection against the possibility of bleeding out.

So stress hormones trigger the production of platelets, a good thing in the short run when your body is anticipating the possibility of a major bloodletting wound, but not such a good thing in the long run. When stress hormones are constantly in the “on” position, you’re *overproducing* platelets. Inevitably, the platelets begin to stick together, and your blood thickens. They combine with other red and white blood cells, as well as with a compound called *fibrin*, to form a kind of “super clot” called a *thrombus*. When a thrombus blocks an artery that leads to the heart muscle, you have a heart attack.

Okay, so what else does your body have to do in a life-threatening emergency to ensure that you stay alive? Divert blood from nonessential areas to essential, check. Make sure you don’t lose any more blood than you absolutely have to by making more platelets so that you can clot more easily, check. But wait! What about *replacing* any blood that you might lose in battle? You’re going to need replacement blood, and where the heck is that going to come from?

Glad you asked.

Heart Attacks Waiting to Happen

Because there are no blood transfusions available in the African Serengeti, you’re going to have to make your own blood. The first thing you’ll need is water, which is found in the kidneys! The kidneys are sitting around, peacefully filtering water and getting ready to send it out into the universe

in the form of urine, but now, with the new demand for water, your stress hormone—fueled body runs down to the kidneys and says, “Wait! Hold the presses! Don’t send that water out into the universe, because we’re gonna need it right here to make more blood!” And because the kidneys really don’t speak English, this message is sent to them via a hormone aptly named the *anti-diuretic hormone*, or ADH, which tells the body to reabsorb water from the kidneys and put it into circulation to increase blood volume.

Brilliant. And it all makes total sense from the point of view of survival.

But what happens when you do this chronically?

Let’s take a look.

See, if you increase the volume of your blood pressure for thirty seconds while you run from a lion, you are one smart dude, from an evolutionary point of view at least. But elevate it for weeks, and you have chronic hypertension. And this is exactly the state that many of us are in today—heart attacks waiting to happen. According to the World Health Organization (WHO), hypertension is one of the most important causes of premature death worldwide, and it’s certainly one of the most important risk factors for heart disease.⁴ Let’s take a look at why.

Stress and Blood Pressure: The Missing Link to Heart Disease

When blood pressure increases, the heart starts pumping blood with more force, pushing the blood vessels outward in response to the sheer power of it. (Imagine a garden hose hooked up to a fully opened fire hydrant. The garden hose would look like it’s about to burst!)

In response to this distending, the blood vessels build up more muscle around them (more layers of rubber on the garden hose), which now makes the vessels more rigid. This in turn requires even *more* pressure to get the blood through them, which means—not surprisingly—your blood pressure goes even higher.

If blood pressure is increased, the heart muscles pay the price. Because blood is being pumped out with more force, it slams back with more force as well. And the area that takes the brunt of this returning blood under high force is the left ventricle. The muscle there begins to enlarge—a condition known as *left ventricular hypertrophy*—and that sets the heart up for irregularities.

Now we'll discuss how this can cause inflammation and trigger the whole chain of events that leads to heart disease, a chain of events in which cholesterol is the most minor of players.

Coming out of your heart is one huge blood vessel called the *ascending aorta*. After a certain distance, this vessel splits into two, a process called *bifurcation*. Each of these two vessels eventually splits into two *more* vessels, which keep bifurcating until you're down to the little capillaries. Now when your blood pressure goes up, the bifurcation—the point where the vessel divides into two—is exactly the spot that gets the brunt of this bashing by the increased force, or blood pressure. Eventually you start to get what's known in physics as *fluid turbulence*. (Think of a tube with fluid moving through it with more and more force; the fluid starts to resemble a miniature version of the water sloshing around a tunnel at a water park.) As the fluid—blood, in this case—slams into the weak spots with increasing force, you get little bits of scarring and tearing, which soon become inflamed. These spots of vessel damage attract more inflammatory cells (such as oxidized LDL cholesterol), which gets into the inflamed areas, sticking to them. Before you know it, you've got plaque.

You've also got damaged blood vessels. Healthy coronary blood vessels *vasodilate* (open) when you need more blood (e.g., when you're running from a saber-toothed tiger). That makes sense—water flows more freely through a fire hose than through a garden hose, and blood flows more easily through a dilated (open) vessel than a constricted (closed) one. But when the coronary blood vessels are damaged, they no longer vasodilate. Just when you need them to open up the most, they actually *close up*, or constrict. Now the heart doesn't get enough blood or oxygen, and you have something called *cardiac ischemia* (lack of oxygen to the heart). The heart muscle isn't getting enough energy, and it hurts. The all-too-familiar name for this pain is *angina*.

And at the core of all this is inflammation.

“Twenty years ago, if you wanted to measure one thing to see how the cardiovascular system was doing, you'd measure your cholesterol,” Sapolsky said. “In recent years people have realized that cholesterol is important, but that *other* things are more important. If you have undamaged vessels there's no place for cholesterol to stick to,” he explained. “If you don't have inflammation, there's no problem.”⁵

VOODOO DEATH

A man wakes in the morning feeling unwell and complains of pain and distress in his chest and abdominal area. He is sweating profusely and gasping for air. His alarmed wife calls 911, but the man dies before the paramedics arrive.

Frequently, the first symptom of heart disease, at least the first symptom that gets *noticed*, is sudden death. (Sudden death tends to get people's attention.) Unfortunately, there is no chastisement, no warning to mend our ways, no trade-off or time to bargain with fate. The heart, omnipotent organ that it is, demonstrates its power over us with one unforgiving defensive maneuver—it attacks us.

Clinical studies have found that from 40 to 50 percent of the time, the first recognized symptom of heart disease is a fatal heart attack, also known as sudden cardiac death (the number one killer of people between the ages of thirty-five and sixty). The big problem with cardiac disease is that it happens with little or no warning. It's literally ominous in its silence. Ninety percent of individuals with heart disease are asymptomatic.

Many of us have heard stories about “voodoo death” (sudden death related to psychogenic stress), a concept researched in detail by the American physiologist Walter B. Cannon, who first introduced the word *homeostasis* and coined the term *fight or flight*. Cannon traveled around the world studying voodoo death in places such as Africa, the Pacific Islands, and Australia. According to Cannon, voodoo death defies the imagination of modern Western man. He cited a case in which a Maori woman died within a day after discovering that she had eaten a piece of fruit that came from a “tabooed” place.

Well, unless you believe that the fruit was cursed or had magical powers, there's clearly another explanation, and it's this: the person's *belief* that the curse was inescapable. A common feature of such a belief, shared by many who believe in the supernatural, is a heightened emotional response. The stress hormones go crazy. The heart pumps blood like sailors bailing out a sinking ship—quickly and furiously. Blood pressure goes through the roof, causing vascular injury. The possessed woman, and other members of her family, believed that she was doomed to die. She had to deal with the sheer,

unmitigated terror of the curse itself, compounded by the fact that she was physically and emotionally isolated. She was all alone in a terrible struggle that eventually ended in death.

But how and why did she die?

Did the social isolation or despair cause a loss of hope and a willingness to die? Or was it the curse itself? Many voodoo deaths are commonly preceded by alienation, isolation, and lack of social support for the person enduring the experience. In the cases that he observed, Cannon concluded that the victims of voodoo death were overcome by terror at the exact moment that they found themselves without the safety net of a supportive environment. The combo was lethal. The victims accepted their deaths as a way to escape an intolerable, miserable situation.

But with all that, there's still no perfect explanation for the physical mechanism of death. What went wrong? Did these people's cholesterol levels suddenly jump?

Here's what Cannon concluded: The overwhelming stimulation of the sympathetic nervous system provokes lethal electrical instability in the heart. In modern terms, doctors would describe this whole "sudden death syndrome" as the result of *malignant arrhythmia culminating in ventricular fibrillation*, or *acute coronary spasms and myocardial infarction*—in other words, a heart attack.

What's important here is not the exact way that the heart fails, but the fact that its breakdown—whatever the specifics—are *precipitated* by a profound loss of hope. Interestingly, Cannon observed that this profound loss of hope was so deep that all attempts to revive these individuals were fruitless.

Once again, we see that psychological belief can determine physical destiny, or at least have a profound influence on it.

Experimental research has demonstrated the impact of acute psychological stress on sudden cardiac death. In one study, 91 percent of patients who experienced sudden cardiac death but were then successfully resuscitated reported that they were experiencing acute psychological stress at the time of their "sudden death" experience. A typical scenario: A middle manager is winding down after a busy week. The economy is in recession. The guy has to cut costs. His overhead is ridiculously high. There's a real

potential of losing his job, and with the loss of his job would come a loss of self-esteem. He is not involved in a loving relationship and is isolated and depressed. He's exercising at his local gym when he hears unexpected and disturbing news. He drops dead suddenly from a massive coronary.

It's not the stressor, per se, that killed him. Under other circumstances—or in another person—disturbing news would be, well, *disturbing*. Not fatal. Much like people who catch colds easily because their immune systems are weak, he is far more susceptible to being hit like a sledgehammer by news that would merely shake a less vulnerable person. In his weakened, vulnerable state, the disturbing news acts like the pesticide carbaryl on a stressed-out frog—it kills him.

We hope we've convinced you that stress isn't just “in your head,” and that the mind and the body operate very much as an integrated unit. A trauma to the body can cause enormous amounts of psychic pain and ultimately even lead to depression or fibromyalgia. And a trauma to the psyche has significant repercussions for the body. They can't be separated, nor should they be. Both are part of the whole person. This is why medicine that looks at the entire person, and how everything is connected, is aptly called *holistic* medicine. (Dr. Sinatra and Dr. Jonny share this orientation; Dr. Sinatra has been practicing “integrative” [holistic] medicine for decades, and Dr. Jonny's Ph.D. is in *holistic nutrition*.)

In this next section, we're going to talk specifically about stress and the impact it can have on your heart and your health. And we'll make recommendations for how you can reduce stress with an easy exercise that anyone can do.

HOW THOUGHTS AND FEELINGS AFFECT YOUR HEART

An essential part of our prescription for heart health involves monitoring and reducing stress, and that means exploring (and expressing) your thoughts and your feelings.

If you want proof that what you think about affects your heart, try this exercise: Sit quietly and peacefully until you feel your breathing calm and your heart rate steady. Concentrate on peaceful words and images. Imagine yourself in a safe, warm, engulfing place—perhaps a favorite beach or even an imaginary tropical island. Stop reading and breathe deeply for a few minutes before continuing to the next paragraph.

Now that you're in this "state," think about something that really disturbs you, maybe a situation at work, or at home, or with your kids or mate. Maybe some incident that caused a great deal of distress in your life, such as a mugging, or the theft of your car, or the death of a loved one. It can even be something that didn't affect you directly—a real-life disaster such as Hurricane Katrina or the BP oil spill. Stop reading for another minute and really feel whatever comes up for you when you think of that disturbing event or situation.

Okay, what happened? Your heart rate probably went up, as did your blood pressure. You might have been able to hear your own heartbeat as it pounded in your ears. You might have felt anxiety and distress mounting in your body. Yet absolutely nothing happened physically. All that changed was your mental state, but this had a noticeable effect on a variety of physical measures.

Years ago, the great neuroscientist Antonio Damasio did a clever experiment that demonstrated how dramatically thoughts affect your body's physiological reactions. He asked Herbert von Karajan, the legendary conductor of the Berlin Symphony, to sit quietly in a chair while hooked up to a variety of devices that monitored heart rate, blood pressure, and brain waves. After getting baseline measurements, he gave von Karajan the score to a Beethoven symphony and asked the conductor to go through it, imagining that he was conducting the orchestra through each passage, but without any significant physical movement. Damasio measured the exact

same changes in brain waves, blood pressure, and heart rate that he had observed when von Karajan actually conducted that same symphony. By merely thinking about and imagining the score, von Karajan's body had responded exactly as it did when he was actually conducting the score.

Overdosing on Adrenaline

Your nervous system can be conveniently described as having two parts, *voluntary* and *involuntary*, which pretty much cover the two major classes of functions that the nervous system performs.

The voluntary nervous system refers to those bodily functions that are under conscious control (doing the tango, knitting, walking, filing your nails, filing your taxes, playing golf, or talking, for example). The involuntary nervous system—technically called the *autonomic nervous system*—is not under conscious control and includes the lion's share of our nervous system and functions (heartbeat, digestion, hair growth, hormone secretion, biochemical release—all the things your body does automatically without your thinking about them). Many of our functions—breathing, for example—run automatically (such as when we sleep), except when we consciously take charge of them (for example, when we “breathe deeply” or “hold our breath”). If this weren't the case, we'd be like the proverbial centipede trying to tell each leg where to go.

Our involuntary functions—those that are for the most part automatic—are very sensitive to our emotions. When we're startled or frightened, the diaphragm, our main breathing muscle, automatically flattens (inhales) and then stays flattened until the emergency is over, and we exhale with a “sigh of relief.” Unfortunately, this is also the case with chronic anxiety. People suffering from anxiety—along with women in labor, or even people with chronic respiratory disease—are taught how to take voluntary control of their diaphragms, inhaling, sighing, or humming to promote exhalation.

The heart is even more vulnerable to our emotions.

Our emotions affect the heart through the autonomic nervous system, which is divided into two opposite and opposing branches. These branches are the *sympathetic nervous system* and the *parasympathetic nervous system*. Ideally, they work together to create a nice state of balance called homeostasis.

The sympathetic system is what prepares us for fight or flight. It's basically responsible for everything that happens once the "warning light" is turned on signaling an emergency. It's the sympathetic nervous system that's responsible for you swerving to avoid an oncoming car or quickly scaling the nearest tree when a wild boar starts charging your campsite. The sympathetic system is in charge of increasing your heart rate and blood pressure while at the same time suppressing "nonemergency" functions such as digestion. The parasympathetic system, on the other hand, is responsible for slowing down. It lowers pulse rate, lowers blood pressure, and stimulates gastrointestinal movements.

Like our ancient ancestors did, we rely on the sympathetic nervous system for extra energy in situations of physical and emotional stress, including combat and athletic events. But such high arousal without an outlet for expression can be damaging. Emotional and psychological arousal (such as fear, dread, worry, and anger) can generate cardiac arrhythmias and coronary artery spasms. They can (and do!) increase blood pressure. And they can even provoke heart attacks and sudden cardiac death.

How does this happen? What life-and-death communications travel between the nervous system and the heart? How can they produce such physiological and pathological responses to both real—and imagined—events?

Well, just as two ordinarily happy partners can have some knock-down, drag-out arguments, in a very real sense the brain and heart can also have some "lethal conversations." Obviously we don't mean that the two organs sit down and have a nice chat over a latte at Starbucks—the communication takes place through the nervous system by way of chemical messengers (hormones!) that literally serve as harbingers of death. Yes, we can even overdose on our own adrenaline in situations that involve fear, horror, excessive arousal, or deep despair and depression. The body can commit suicide by overstimulating the heart. And the heart running wildly in panic mode terminates with ventricular fibrillation.

So the brain and the heart are in constant communication. There's definitely a heart-brain "hotline." Identifying people at risk for sudden death depends on identifying not only the traditional risk factors for heart disease but also psychological and emotional elements.

Thoughts, unconscious and conscious, appear to be critical factors that link our “personalities” with the centers of the brain that control the functions of the heart. These are the hidden emotional risk factors for heart disease. And they’re far more important than cholesterol is!

Denial Ain’t a River in Egypt

Some people truly don’t feel the pain of their symptoms because, frankly, they’re living in denial, which, for our purposes, we’ll define as a state of being cut off from the awareness of what is happening to your body. Living in denial—out of touch with your body and its feelings—often leads to disaster. You fail to admit that a problem exists. Or you believe your symptoms are “nothing,” or something very “minor.” (Steve has seen this situation time and time again in many coronary-prone patients who told him they were experiencing indigestion when in fact they were having a heart attack.)

Take, for example, the case of Jim.

Jim was a banker, opening up a checking account for a new client, as he had done many times in the past. The client had a bunch of questions, all of which Jim answered patiently. But the client persisted with more questions and concerns. Jim had another client waiting and began to feel trapped.

He probably should have told his client that he had someone else waiting and that they’d have to continue another time. But instead—as is typical in many type-A men—he withheld his emotions and frustrations. He was feeling so much stress that he had to wipe the sweat off his brow.

Jim totally denied this bodily sensation, as well as all the other obvious messages his body was sending him. His hands began to sweat. He had difficulty breathing. He became dizzy, and he experienced chest pains.

Thinking the pain was just indigestion, Jim didn’t let anyone around him know how he was feeling. Fifteen minutes later, Jim was brought to the emergency room after suffering a heart attack.

Thus, a seemingly everyday occurrence ended in tragedy. But why? Why does a man put so much strain on his body that he ends up in total collapse?

The answer is simple. Jim was living in denial.

Living with awareness about your body is really the key to preventing ill health. Jim denied all the signals his body was sending him. (Although we

can't know for sure, it's a safe bet to say that Jim's lifelong habit of repressing his feelings was a strong contributing factor to his heart attack.) Instead, he pushed beyond his normal expectations and almost died in the process. Jim was really out of touch with his body. He really didn't listen to any of the "conversations" that went on between his brain and his heart. The mind saying one thing while the body is saying another is at the root of what cardiologists call *silent myocardial ischemia* (a lack of blood flow to the heart, which often results in damage to the heart muscle). The EKG tells us the heart is in trouble, even though the patient has no sensation. But the body is telling the truth, as the heart reveals its distress.

No one questions that there are strong behavioral and psychological factors that frequently precipitate cardiac arrest. It's no coincidence that sudden psychological or emotional stress frequently occurs just prior to a heart attack. It's well documented that Monday morning, the day most people go back to work after a weekend away, is the most common time for sudden cardiac death. Approximately 36 percent of all sudden deaths occur on Monday! And interestingly, the second most common time is Saturday. Why? Could it be the result of psychologically and emotionally gearing up (Monday) or gearing down (Saturday)? Is the office a safe place? Or is it a place of combat and stress (especially for the heart)? Look, some people may loathe going to work, but others may loathe going home. Whatever the stress is, the heart will reveal it. And the heart will tell the truth about it.

Dr. Sinatra:

I remember the unfortunate case of a fifty-two-year-old diabetic woman who had spontaneously bled into her eye and required emergency surgery. Two years before, she had sustained a heart attack but had since enjoyed a good quality of life. She was not experiencing any symptoms of chest pain or shortness of breath, and there were no other obvious signs of heart problems. She was admitted to the hospital and underwent immediate surgery that was, unfortunately, unsuccessful.

Upon learning of the loss of her eyesight, she became deeply saddened and depressed. (Who wouldn't be?) I remember seeing her in the hospital ward and feeling her depth of sorrow. Sitting in a wheelchair, she was despondent that she couldn't see. She talked in a monotone voice and kept her head down. She said that she had lost all hope and had nothing to look forward to.

She died a day later.

STRESS AND CHOLESTEROL

Your doc may tell you to fast before certain blood tests, but we'll bet that no doc ever told you to meditate before taking a cholesterol test. Now granted, we don't think cholesterol test results are important (*unless* you get the particle size test we recommended earlier). But your doctor undoubtedly *does*. And he or she would probably be surprised to learn that stress can actually influence those cholesterol test results. After all, how could stress—which clearly originates in the brain—influence something like cholesterol in the bloodstream?

Glad you asked. Here's what Dr. Sinatra has to say:

Some years ago, I was asked to submit to a fasting serum cholesterol test for an insurance evaluation. Because I was performing three cardiac catheterizations that day, I asked that blood be drawn prior to 7:30 in the morning.

At that time, my blood cholesterol was 180 mg/dL, a number my doctors and I were utterly delighted with. After performing two of the three cardiac catheterizations, both of which went smoothly, I tackled the third case, which was anything but routine. This was an individual with complex congenital heart disease. The cardiac catheterization itself was further complicated by the fact that during the procedure, the patient suffered cardiac arrest. The patient actually stopped breathing, though, luckily, he was successfully resuscitated. The procedure took a grueling five hours, and it required multiple catheters and multiple pharmacological interventions.

Man, I really sweated during that case, even though, thankfully, it all ended well.

When the procedure was over, it was approximately three in the afternoon, and I hadn't eaten all day. As I was walking to the cafeteria, I passed the blood lab where I had blood drawn earlier that morning. Because I had a strong belief in the effect of psychological stress on the body, I was curious to see whether the day's activities had produced any changes in my own blood. So I asked my colleagues to perform a second blood test.

My blood cholesterol had risen to 240 mg/dL, a number that would cause virtually any conventional practitioner to put me on a statin drug

immediately.

I had been fasting for nearly 20 hours at this point, and there was absolutely no dietary variable that could have caused this jump of 33 percent in my cholesterol. Obviously, my body reacted to the stressful events of the day by producing an excessive amount of cholesterol.

The connection between stress and elevated cholesterol is well documented. In 2005, researchers conducted a study of about 200 middle-aged government workers in London.⁶ First the workers gave blood samples and “rated” their levels of stress. Then they were given two paper and pencil tests, both designed to be somewhat stressful. In the first test, they were shown mismatched words and colors. For example, the word “red” would be written in blue letters. The participants had to name the color in which the words appeared (in this case “blue”). It’s a confusing and annoying test and makes people uneasy. In the second test, the participants were told to trace the outline of a star in a mirror, under a deadline. (Try it sometime—it’ll make you crazy.) Afterward, the participants gave blood again, had their cholesterol checked, and rated their stress levels.

Three years later everyone had their cholesterol levels measured again.

The first finding was interesting on its own: Cholesterol rose for everyone after doing the stress-inducing paper and pencil tests. But it rose for some people a lot more than it did for others. Let’s call them the “high reactors.”

Now check this out: Three years later, the high reactors had the highest cholesterol levels.

The researchers created three “thresholds” for cholesterol: low, medium, and high. After the three years, those who hit the “high cholesterol” threshold included 16 percent of those who had initially shown little cholesterol reaction to the stress tests and 22 percent of those who had initially shown a “moderate” cholesterol reaction to the stress tests.

But a whopping 56 percent of those who initially had the biggest change in their cholesterol after the stress tests were now in the “high cholesterol” group! And this was even after making adjustments for weight, smoking, hormone therapy, and alcohol use.

The short stress tests were excellent predictors of how people—and their cholesterol levels—responded to stress. “The cholesterol responses we measured in the lab probably reflect the way people react to challenges in everyday life,” said lead researcher Andrew Steptoe, D.Sc. “The larger cholesterol responders to stress tasks will be large responders to emotional situations in their lives,” he added. “It is these responses in everyday life that accumulate to lead to an increase in fasting cholesterol . . . three years later. It appears that a person’s reaction to stress is one mechanism through which higher [cholesterol] levels may develop.”⁷

Stress and Depression

Stress is certainly a trigger for depression, and the relationship between depression and heart disease is well established. Individuals who suffer from mood disorders are twice as likely to have a heart attack when compared to people who are not depressed.

One researcher who has spent much of his career investigating the relationship between depression and heart disease is Alexander Glassman, M.D., a professor of psychiatry at Columbia University and chief of clinical psychopharmacology at New York State Psychiatric Institute. In a number of published studies, he has shown that medically healthy but clinically depressed patients are at increased risk of both cardiovascular disease and cardiac death. Depression following a heart attack especially increases the risk of death.⁸ “It is now apparent that depression aggravates the course of multiple cardiovascular conditions,” he wrote.⁹

The Stress of Sorrow

If we look at those suffering a bereavement, sudden death is two to ten times higher than in the general population. It’s even worse if a man loses his wife than if a woman loses her husband. In general, women adapt better than men do. Women express feelings more often. They find joy in sharing those feelings, especially with other women. They form networks and nurture each other. Men, on the other hand, build walls. They hold feelings in. They keep secrets and sometimes have a really hard time communicating.

Dr. Sinatra:

As trite as it sounds, love heals.

In my “Healing the Heart” workshops, we see profound cholesterol lowering when a patient experiences contact and connectedness in a supportive environment. In these four-to seven-day workshops, cholesterol levels have been lower in every one of our participants, with some losing as much as 100 mg/dL of cholesterol in just a few days!

The dramatic reduction in cholesterol supports the notion that emotional contact can positively affect our health.

Once, during a workshop, a physician from Greece was asked about the relative lack of heart disease in Crete and Greece. He immediately responded by speaking of the healing powers of nurturing relationships, particularly among the males. He described how men in Crete spend quality time with one another, talking over lunch about real feelings. The typical topics discussed when American men get together—sports, politics, and money—just aren’t central in their conversations. They talk about feelings. They talk about their families. They talk about their dreams and even their spiritual beliefs. And they rarely wear “social masks.” Instead, they argue, cry, support, and even hold each other. The Greek doctor felt that such camaraderie—occurring often over games of chess or during two-hour lunches—is a major factor in the reduction of coronary heart disease.

Maybe part of the “secret” of the Mediterranean diet isn’t the diet at all. Maybe it has something to do with how the people in the Mediterranean live.

When you support and nurture yourself, your positive self-esteem reflects itself in the healing of your body.

Although digging into your emotions and allowing yourself to be vulnerable can be difficult if you are unaccustomed to such soul-searching, we invite each of you to consider looking more deeply into your emotional self. Such introspection can initially be painful, but it is well worth the effort in the long run. When you support and nurture yourself, your positive self-esteem reflects itself in the healing of your body. Such nurturing and protective influences have been validated in studies time and time again.

Animals and the Stress of Heartbreak

If you're an animal lover like we are, you might not want to read the next few paragraphs. We're going to tell you about a horrible and sad study that nonetheless dramatically illustrates the role of psychological stress in heart disease and death. (Don't say we didn't warn you.)

Baboons are some of the most lovable creatures on earth. They sleep and travel in groups of about fifty individuals. They're highly social and very connected. Adults sit in small groups grooming one another while the youngsters romp and play. They forage for about three hours in the morning, rest during the afternoon, and then forage again later on before returning to their sleeping places. Before bed, they spend more time grooming each other, which not only keeps them clean and free of external parasites, but also serves to strengthen their bonds. And they're ambassadors for "family values"—they mate for life.

Early in the twentieth century, Soviet experimenters performed the following experiment. They reared eighteen baboon couples together, and then, after the bonds were strongly established, they removed the male from the cage and replaced him with a new male. The ex-mate was placed only a few feet away in another cage, fully able to observe his former partner and her new "mate."

Within six months, every one of the eighteen "ex-husbands" died.

Technically, they died of strokes, hypertension, and heart attacks. Less technically, we could say they died of heartbreak. Either way, the acute psychological stress of being trapped, heartbroken, and, most important, helpless to do anything about it, overwhelmingly resulted in death.¹⁰

Dr. Jonny:

Warren Buffett is a particular hero of mine, but not because he's the richest dude in America. Rather, I admire him because, by all accounts, he is remarkably down-to-earth, unpretentious, compassionate, and unafraid of expressing his feelings—not exactly a constellation of traits most of us associate with incredible wealth and power.

Much of this probably has to do with Susie.

Susie met Buffett in 1950, and they were married two years later. “She put me together,” he said.¹¹ Susie was big on civil rights and fairness. She was involved in helping the cause of integration in Omaha back in the 1960s and influenced Buffet so much that he became active in overturning anti-Semitic membership rules at the fancy Omaha Club. She humanized him.

Prior to meeting Susie there was little time in Buffet's life for anything but moneymaking. Although they eventually separated, they shared a great love, and it was probably the most transformative relationship of Buffett's life. Susie even introduced him to her friend Astrid, who, with Susie's blessing, eventually became his mistress and, after Susie's death, his second wife.

Seven years after Susie's death, Buffett was the subject of a *Time* cover story by Rana Foroohar.¹² When discussing Susie, he burst into tears. Foroohar reported that it took several moments for him to recover. She put her hand on his arm. “Eventually,” she said, “we moved on to an easier subject—his investments.”

Few men of Buffett's station in life would allow themselves to feel vulnerable enough to break down and cry in front of a reporter when talking about the love of their life. In fact, few men of any station in life would feel free enough—and be in touch with their feelings enough—to do so.

Buffett eats a horrific diet of fast food, is reported to drink about 60 ounces (1.7 liters) of Coca-Cola a day, and has never been seen at a gym. Yet at eighty-one, he's sharp, active, involved, and engaged.

He's also healthy.

Could his dyed-in-the-wool optimism coupled with his ability to express his feelings easily and relate to people deeply be profoundly protective of his heart?

Food for thought.

CHAPTER 9

PUTTING IT ALL TOGETHER—A SIMPLE AND EASY BLUEPRINT FOR A HEALTHY HEART—AND LIFE!

IN THIS CHAPTER, we're going to make specific suggestions about what you can do right now to prevent a first (or second) heart attack and keep your heart healthy for many decades.

We're going to advise you about which tests you should ask your doctor for and why. We'll recommend which foods you should incorporate into your diet, if you haven't already.

And we're also going to discuss the emotional and psychological risk factors for heart disease, which need to be taken just as seriously as the physical ones. We'll give you specific tools to help lower these risk factors.

THE TESTS YOU SHOULD ASK YOUR DOCTOR FOR

We hope by now you're convinced that total cholesterol is a meaningless number and should be the basis for absolutely nothing in your treatment plan. The old division into "good" (HDL) cholesterol and "bad" (LDL) cholesterol is out of date and provides only marginally better information than a "total" cholesterol reading. As we've said, both good and bad cholesterol have a number of different components (or subtypes) that behave quite differently, and the twenty-first-century version of a cholesterol test should always tell you exactly which subtypes you have. Anything less is not particularly useful and should never be the sole basis on which a treatment plan or a statin drug is recommended. That's why the LDL particle size test is the first test we recommend.

1. Particle Size Test

Although LDL cholesterol is known as the "bad" cholesterol, the fact is that it comes in several shapes and sizes, as does HDL cholesterol, the so-called "good" kind. These different subtypes of cholesterol behave very differently. Seen under a microscope, some LDL particles are big, fluffy, and harmless. Some are small, dense, "angry," and much more likely to become oxidized, slipping through the cells that line the walls of the arteries (the endothelium) and beginning the inflammatory cascade that leads to heart disease.

Tests are now available that measure LDL particle size, and that's the information you really want to have. If you have a pattern A cholesterol profile, most of your LDL cholesterol is the big, fluffy kind, which is great; but if you have a pattern B profile, most of your LDL cholesterol is composed of the small, dense, atherogenic particles that cause inflammation and ultimately plaque. (Fortunately, you can change the distribution from small to buoyant by following the dietary and supplement recommendations in this book.)

One widely used test is called the **NMR LipoProfile**, and it analyzes the size of LDL particles by measuring their magnetic properties. Others—including the **Lipoprint** and the **Berkeley** (from the Berkeley HeartLab)

use electrical fields to distinguish the size of the particles. Another test known as the **VAP** (Vertical Auto Profile) separates lipoprotein particles using a high-speed centrifuge.¹ And still another is the **LPP** (or Lipoprotein Particle Profile). Any of these newer cholesterol tests can be offered by your doctor.

Taking a statin drug, or any other medication, based solely on the standard cholesterol test is a really bad idea. Ask your doctor for one of the newer particle tests. If he objects, make sure he has a darn good reason. It's the only cholesterol test that matters.

2. C-Reactive Protein (CRP)

CRP is a marker for inflammation that is directly associated with overall heart and cardiovascular health. In multiple studies, CRP has been identified as a potent predictor of future cardiovascular health—and, in our opinion, one that is far more reliable than elevated cholesterol levels. Biological characteristics that are associated with high CRP levels include infections, high blood sugar, excess weight, and hypercoagulability of blood (sticky blood).

Fortunately, there is a simple test that your doctor can conduct to find out how much CRP is in your blood. Just make sure the high-sensitivity test (**hs-CRP**) is used. This test doesn't take much time: Typically, blood is drawn from a vein located either on your forearm or on the inside of your elbow. The blood is then analyzed in several tests to determine the level of CRP present. (Dr. Sinatra's recommendation for an optimal CRP level is less than 0.8 mg/dL.)

3. Fibrinogen

Fibrinogen is a protein that determines the stickiness of your blood by enabling your platelets to stick together. You need adequate fibrinogen levels to stop bleeding when you've been injured, but you also want to balance your fibrinogen levels to support optimal blood circulation and prevent unnecessary clotting. (In women younger than forty-five, Dr. Sinatra has seen far more heart attacks caused by improper blood clotting than by anything else.) Normal levels are between 200 and 400 mg/dL, and they may be elevated during any kind of inflammation.

Fibrinogen has been identified as an independent risk factor for cardiovascular disease and is associated with the traditional risk factors as well. In one study, fibrinogen levels were significantly higher among subjects with cardiovascular disease than among those without it.²

There are two ways to test for fibrinogen. The first is the **Clauss method** and the second is a newer test called the **FiF** (immunoprecipitation functional intact fibrinogen) test, which was developed by American Biogenetic Sciences.³ The FiF test is the better one because it shows a stronger association with cardiovascular disease than the Clauss method does.⁴ If the FiF test isn't available, use the Clauss method—it still has a strong association with cardiovascular disease, even if it's not quite as accurate as the newer test.

If you have a family history of heart concerns, you must check your serum fibrinogen level. Women who smoke, take oral contraceptives, or are postmenopausal usually have higher fibrinogen levels.

Worth noting: This test hasn't caught on with many doctors because there are no direct treatments for elevated levels. But supplements such as nattokinase, discussed in [chapter 7](#) on supplements, can work well to “thin” the blood and prevent unwanted clotting. Adding omega-3 fatty acids to your diet may also help.

4. Serum Ferritin

Ever wonder why so many vitamin manufacturers offer multiple vitamins “without iron”? Here's why: Iron is one of those weird substances where if you don't have enough you can have some real problems (e.g., iron-deficiency anemia), but if you have too much, look out! Iron is highly susceptible to oxidation. (Imagine someone leaving a barbell from your gym outside in the rain for a couple of days. It's going to rust like crazy. That's oxidation.)

Iron levels in the body are cumulative (stored in the muscles and other tissues), and unless iron is lost through menstruation or by donating blood, over the years toxic levels can build up in the system. Although this danger always exists for men, it becomes a real risk for women after menopause. Both of us are adamant that no one but premenopausal women should ever

take vitamins with iron, or supplemental iron of any kind, unless prescribed by a doctor.

Iron overload—technically called *hemochromatosis*—can actually contribute to heart disease. Researchers measure iron in the blood by measuring a form of it called *ferritin*. A 1992 study by Finnish researchers examined the role of iron in coronary artery disease. After studying 1,900 Finnish men between the ages of forty-two and sixty for five years, the researchers found that men with excessive levels of ferritin had an elevated risk of heart attack, and that every 1 percent increase in ferritin translated into a 4 percent increase in heart attack risk.⁵

Those with high levels of ferritin were more than twice as likely to have heart attacks than those with lower levels. The authors of this study concluded that ferritin levels may be an even stronger risk factor for heart disease than high blood pressure or diabetes is.⁶ It's certainly a more important risk factor than high cholesterol.

If your ferritin levels are high, consider donating blood every so often, or ask your doctor to consider a therapeutic phlebotomy. (Dr. Sinatra's recommendation for an optimal serum ferritin level is less than 80 mg/L for women and less than 90 mg/L for men.)

Worth noting: One consideration regarding supplemental vitamin C is that it helps the body absorb iron better. If you have a problem with iron levels, keep your supplemental vitamin C to less than 100 mg a day.

5. Lp(a)

Lp(a) is a type of cholesterol-carrying molecule that contains one LDL (low-density lipoprotein) molecule chemically bound to an attachment protein called *apolipoprotein(a)*. In a healthy body, Lp(a) isn't much of a problem. It circulates and carries out repair and restoration work on damaged blood vessels. The protein part of it promotes blood clotting. So far, so good.

The problem is, the more repair you need on your arteries, the more Lp(a) is utilized, and that's when things get ugly. Lp(a) concentrates at the site of damage, binds with a couple of amino acids within the wall of a damaged blood vessel, dumps its LDL cargo, and starts to promote the

deposition of oxidized LDL into the wall, leading to more inflammation and ultimately to plaque.

Also, Lp(a) promotes the formation of blood clots on top of the newly formed plaque, which narrows the blood vessels further. If the clots are large enough, they can block an artery. (Most heart attacks are due to either a large clot developing in vessels with moderate-to-severe narrowing or a plaque rupture that blocks the artery.)

Elevated Lp(a) is a very serious risk factor. A very high percentage of heart attacks happen to people with high Lp(a) levels. Dr. Sinatra thinks Lp(a) is one of the most devastating risk factors for heart disease and one of the hardest to treat.

One reason doctors aren't running out to test for Lp(a) all the time is that there are no real pharmaceutical interventions that work to lower it. In addition, Lp(a) levels are largely genetically determined and not very modifiable by lifestyle choices. However, your Lp(a) level can give you a good idea of your real risk for heart disease, and a high level may serve as a wake-up call to inspire you to work harder to improve your heart health using the strategies, foods, supplements, and lifestyle changes suggested in this book. That said, Dr. Sinatra feels that Lp(a) can be lowered with a combination of 1 to 2 g of fish oil, 500 to 2,500 mg of niacin (not the slow-release kind), and 200 mg of lumbrokinase.

Worth noting: Statin drugs can sometimes raise Lp(a) levels! This is mentioned on the warning labels of statin drug ads in the Canadian edition of the *New England Journal of Medicine*, but such labeling is not required by the Food and Drug Administration, so you won't see it in ads published in the United States.⁷

6. Homocysteine

Homocysteine is an amino acid by-product that causes your body to lay down sticky platelets in blood vessels. Having some homocysteine is normal, but an excess might affect your cardiovascular health. Evidence shows that homocysteine contributes to atherosclerosis, reduces the flexibility of blood vessels, and helps make platelets stickier, thus slowing blood flow. Net result: There's a direct correlation between high homocysteine levels and an increased risk of heart disease and stroke.

Elevated homocysteine strongly predicts both a first and a recurring cardiovascular incident (including death).⁸ Too much homocysteine adversely affects the function of the endothelium, the all-important lining of the artery walls. It also increases oxidative damage and promotes inflammation and thrombosis—a regular evil trifecta for heart disease.⁹ One study looked at more than 3,000 patients with chronic heart disease and found that a subsequent coronary event was 2.5 times more likely in patients with elevated levels of homocysteine. What’s more, each 5 $\mu\text{mol/L}$ of homocysteine predicted a 25 percent increase in risk!¹⁰

Fortunately, there’s an easy way to bring down homocysteine levels. All you have to do is give the body the three main nutrients it needs to metabolize homocysteine back into harmless compounds. The three nutrients are folic acid, vitamin B₁₂, and vitamin B₆. All it takes is about 400 to 800 mcg of folic acid, 400 to 1,000 mcg of B₁₂, and 5 to 20 mg of B₆. If you’ve had a heart attack or other cardiovascular event; if you have a family history of early heart disease; or if you have hypothyroidism, lupus, or kidney disease, consider asking your doctor to test your homocysteine levels. Finally, if you take drugs that tend to elevate homocysteine—theophylline (for asthma), methotrexate (for cancer or arthritis), or L-dopa (for Parkinson’s)—you should be tested. (Dr. Sinatra’s recommendation for an optimal homocysteine level is between 7 and 9 $\mu\text{mol/L}$.)

7. Interleukin-6

Interleukin-6 is important because it stimulates the liver to produce CRP. And we are learning that this inflammatory cytokine has a strong association with not only heart disease but also asthma. (Asthma is the result of airways swelling and constricting, so it makes sense that an inflammatory agent is behind the curtains here as well.) The Iowa 65+ Rural Health Study demonstrated that elevated levels of interleukin-6 and CRP were associated with an increased risk for both cardiovascular disease and general mortality in healthy older people.

Interleukin-6 may be an even better marker for inflammation than CRP is because these “precursor” levels rise earlier. If you’re concerned about inflammation and its effect on your heart, ask your doctor to do an

interleukin-6 test. (Dr. Sinatra's recommendation for an optimal interleukin-6 level is 0.0 to 12.0 pg/mL.)

8. Coronary Calcium Scan

Calcium is great—as long as it stays in the bones and teeth. One place you don't want it is in the coronary arteries.

Coronary calcification is one of the major risk factors that predicts coronary heart disease and future heart attacks.¹¹ The more calcium present, the greater the risk of suffering a heart attack. Men develop calcifications about ten to fifteen years earlier than women do. Calcification can be detected in the majority of asymptomatic men over fifty-five years of age and in women over sixty-five.

As far back as 1991, cardiologist Stephen Seely, M.D., published a paper in the *International Journal of Cardiology* titled "Is Calcium Excess in the Western Diet a Major Cause of Arterial Disease?" He pointed out that cholesterol only makes up 3 percent of arterial plaque while calcium makes up 50 percent!¹²

The Florida cardiologist Arthur Agatston, M.D., is best known for his wildly popular South Beach diet, but what many people don't know is that he also developed a widely accepted test for coronary calcification known as the **Agatston test**. Individuals who score less than 10 on the Agatston test have minimal calcification; those with Agatston scores of 11 to 99 have moderate calcification; those with scores of 100 to 400 have increased calcification; and those with scores above 400 have extensive calcification.

It is well established that individuals with Agatston scores above 400 have an increased occurrence of coronary procedures (bypass, stent placement, and angioplasty) and events (myocardial infarction and cardiac death) within the two to five years following the test. Individuals with very high Agatston scores (over 1,000) have a 20 percent chance of suffering a heart attack or cardiac death within a year. Even among patients over the age of seventy who frequently have calcification, an Agatston Score above 400 was associated with a higher risk of death.¹³

The American Heart Association and the American College of Cardiology provide guidelines for coronary calcification testing, available online, www.ahajournals.org/misc/sci-stmts_topindex.shtml. These

guidelines currently suggest—and we agree—that screening for calcification is of value for an individual who is considered to be at intermediate ten-year risk, which means that he or she has a 10 to 20 percent likelihood of experiencing a cardiac event within the next ten years.¹⁴

◀ WHAT YOU NEED TO KNOW

Ask your doctor for the following tests, which are more important than the standard test for cholesterol:

- LDL particle size
- Hs-CRP
- Fibrinogen
- Serum ferritin (iron)
- Lp(a)
- Homocysteine
- Interleukin-6
- Coronary calcium scan

Eliminate these foods:

- Sugar
- Soda
- Processed carbs
- Trans fats
- Processed meats
- Excess vegetable oils

Eat more of these foods:

- Wild salmon
- Berries and cherries
- Grass-fed meat
- Vegetables
- Nuts

- Beans
- Dark chocolate
- Garlic and turmeric
- Pomegranate juice, green tea, and red wine
- Extra-virgin olive oil

Make these lifestyle changes to reduce stress:

- Meditate or practice deep breathing
- Express your emotions
- Play
- Cultivate intimacy and pleasure
- And most of all . . . enjoy your life!

EAT THIS, DUMP THAT

This section is divided into two parts—what to eat and what *not* to eat for optimal heart health. Fortunately, the list of what not to eat is fairly short, so let's get that one out of the way first. We call it the “Dump It!” list and provide you with specific “fast action plans” to help you remove these nutritionally empty, heart-unfriendly foods from your diet. The second section is called “Eat This!” and reveals some of the healthiest foods on the planet.

Dump It: Sugar

As we've said throughout this book (see [chapter 4](#)), sugar is a far worse threat to your heart than fat ever was.

The 2010 Dietary Guidelines for Americans suggest that no more than 25 percent of your calories should come from added sugars, but we think that's a ridiculously high amount. (The American Heart Association recommends no more than 5 percent.) Research by Kimber Stanhope, Ph.D., at the University of California, Davis, has shown that when people consume 25 percent of their calories from fructose or high-fructose corn syrup, several factors associated with an increased risk for heart disease—including triglycerides and a nasty little substance called *apolipoprotein B*—escalate.¹⁵ (Remember, it's the fructose in sugar that's the problem. High-fructose corn syrup is 55 percent fructose, and regular sugar is 50 percent fructose, so for all intents and purposes, they have the same bad effect on your heart and your health.)

Fast Action Plan: Cut out soda. Soda is probably the worst offender in this category, but not by much. Fruit juices are loaded with sugar and only marginally better than soda. “Energy drinks” aren't any better. Most are loaded with sugar, and the sugar-free versions are loaded with chemicals. Many processed carbs (see below) are also full of sugar, and virtually all cakes, candies, pastries, doughnuts, and other sources of empty calories are also sugar heavyweights.

Dump It: Processed Carbohydrates

Processed carbs include almost any carbohydrate food that comes in a package: cereals, pasta, bread, minute rice, you name it. These foods are almost always high-glycemic, meaning they quickly and dramatically raise your blood sugar, which is exactly what you do not want. A 2010 study in the *Archives of Internal Medicine* demonstrated that women who ate the highest amount of carbohydrates had a significantly greater risk of coronary heart disease than those who ate the lowest amount, and that carbohydrates from high-glycemic carbs were particularly associated with significantly greater risk for heart disease.¹⁶ (This association was not confirmed for men in this particular study, but we suspect that future studies will discover that it's true for both sexes.)

CORNFLAKES A GREAT BREAKFAST? THINK AGAIN!

If any of you out there still think cornflakes are a great, wholesome breakfast, read on.

A landmark research study conducted by Michael Shechter, M.D., of Tel Aviv University's Sackler School of Medicine and the Heart Institute of Sheba Medical Center, with collaboration from the Endocrinology Institute, shows exactly how high-carbohydrate foods increase the risk for heart problems.¹⁷

Researchers looked at four groups of volunteers who were given different breakfasts. The first group was given a cornflake mush mixed with milk, not unlike the typical American breakfast. The second group was given a pure sugar mixture. The third group was given bran flakes. And the fourth group was given a placebo (water).

Over four weeks, Shechter applied a test that allows researchers to visualize how the arteries are functioning. It's called *brachial reactive testing*, and it uses a cuff on the arm (similar to those used for measuring blood pressure) that can visualize arterial function in real time.

The results were dramatic. Before any of the patients ate, their arterial function was basically the same. After eating, all had reduced functioning except for the patients in the water-drinking placebo group. Enormous peaks indicating arterial stress were found in the high GI groups: the cornflakes and sugar groups.

"We knew high glycemic foods were bad for the heart. Now we have a mechanism that shows how," Shechter wrote. "Foods like cornflakes, white bread, French fries, and sweetened soda all put undue stress on our arteries. We've explained for the first time how high-glycemic carbs can affect the progression of heart disease."

During the consumption of foods high in sugar, there appears to be a temporary and sudden dysfunction in the endothelial walls of the arteries. Endothelial health can be traced back to almost every disorder

and disease in the body. According to Shechter, it is the “riskiest of the risk factors.”

Shechter recommended sticking to foods such as oatmeal, fruits and vegetables, and legumes and nuts, which all have a low glycemic index. Exercising every day for at least thirty minutes, he added, is an extra heart-smart action to take.

There’s no two ways about it—high-glycemic carbohydrates are inflammatory. As researchers from Harvard Medical School and the Harvard School of Public Health noted, quickly digested and absorbed carbs (i.e., those with a high glycemic load) are associated with an increased risk of heart disease.¹⁸

These same researchers examined the diets of 244 apparently healthy women to evaluate the association between glycemic load and blood levels of CRP (C-reactive protein, the systemic measure of inflammation discussed earlier in this chapter). They found “a strong and statistically significant positive association between dietary glycemic load and [blood levels of] CRP.”¹⁹ And that’s putting it mildly. Women whose diets were highest in glycemic load had almost twice the amount of CRP in their blood as women whose diets were lowest in glycemic load (3.7 for high-glycemic load ladies, 1.9 for low-glycemic load ladies). The difference in inflammation levels was even more pronounced for overweight women. Among women with a body mass index (BMI) greater than 25, those whose diets were lowest in glycemic load had an average CRP reading of 1.6, but those whose diets were highest in glycemic load had a CRP reading more than three times that amount (average measurement: 5.0 mg/L).²⁰

Full disclosure: We don’t much buy into the argument that “whole grains” eliminate all the problems associated with processed carbs, and here’s why: Number one, most commercial products that are made with whole grains don’t contain all that much of them. Number two, whole grains raise blood sugar almost as much as processed grains do. Number three, whole grains still contain gluten, which can be very inflammatory for people who are gluten-sensitive. That said, real whole grain products (Ezekiel 4:9 breads, for example) are way better than their processed

counterparts. But be a careful consumer—just because a label says “wheat” instead of “white,” don’t assume it’s good for you.

Fast Action Plan: Reduce (or eliminate) consumption of processed carbohydrates. At the same time, increase non-processed carbohydrates such as vegetables and low-sugar fruits. Replace your bagel and orange juice with some eggs, veggies, and a slice of avocado. Have berries for dessert. When eating out, say “no” to the breadbasket.

Dump It: Trans Fats

According to findings presented at the annual meeting of the American Heart Association in 2006, women who ate the most trans fats were more than three times as likely to develop heart disease as women who ate the least.²¹ Harvard researcher Charlene Hu examined data from the long-running Nurses’ Health Study, which has followed 120,000 female nurses for more than thirty years. His research shows that for each 2 percent increase in trans fat calories consumed, the risk for coronary heart disease roughly doubles!²² Trans fats raise LDL cholesterol levels, which doesn’t mean very much by itself, but at high intakes they also reduce HDL levels, which definitely isn’t good.²³

The worst offenders include nondairy “creamers,” most margarines, cake mixes, ramen noodles, soup cups, virtually all packaged baked goods (e.g., Twinkies, chips, and crackers), doughnuts, many breakfast cereals, “energy” bars, cookies, and definitely fast food. (Just for example, a medium order of fries contains an incredible 14.5 g of trans fat, and a Kentucky Fried Chicken Original Recipe chicken dinner has 7 g. The ideal intake for humans is 0 g.)

THE “NO TRANS-FATS!” SCAM

When the government mandated that trans fats be listed on the nutrition facts label of food, big food lobbyists sprang into action. They somehow created a loophole that lets manufacturers use trans fats while legally claiming “no trans fats!” on their packaging. Here’s how:

Manufacturers can claim “no trans fats” as long as there is less than half a gram of the stuff per serving. Sounds reasonable, until you remember how clever and ruthless Big Food can be. By making “serving sizes” ridiculously small, and by keeping trans fats to just under half a gram per “serving,” they were able to technically comply with the rules. But the end result is that if each artificially small “serving” contains, say 0.4 g of trans fats, you could quite easily consume a gram or two of the stuff just by eating what most people would consider a “normal” serving size. Do that a few times a day and before you know it you’ve raised your heart disease risk by quite a few percentage points.

What to do? Simple. Ignore the “no trans fats!” legend on the front of the package and read the ingredients list instead. No matter what the label says, if the list of ingredients contains partially hydrogenated oil or hydrogenated oil, the product has trans fats. Period. (Typically, you’ll see partially hydrogenated soybean oil in the ingredients list, but it could be any type of oil at all. What you’re looking for are the keywords *hydrogenated* and *partially hydrogenated*.)

Worth knowing: There is one exception to the don’t-eat-trans-fats rule, and that’s something called *conjugated linoleic acid*, or CLA. CLA is a trans fat that’s not man-made; rather, it’s made naturally in the bodies of ruminants (cows). Factory-farmed meat doesn’t have any, but grass-fed meat—and products that come from pasture-raised animals—do. CLA has both anticancer and antiobesity properties. CLA is good for you, unlike hydrogenated or Partially hydrogenated oils—the very definition of man-made trans fats—which are definitely *not* good for you.

Fast Action Plan: Stop eating fast food. On all packaged foods from the supermarket, check the ingredients list for “partially hydrogenated” or “hydrogenated” oils. If either of those is listed, don’t eat it. Look in particular at margarines, cookies, cakes, pastries, doughnuts, and, as mentioned, fast food.

Dump It: Processed Meats

Processed meats contribute to both inflammation in general and heart disease specifically.

Harvard researchers investigated the effect of eating processed meat versus unprocessed meat. Processed meat was defined as any meat preserved by curing, salting, smoking, or with the addition of chemical preservatives, such as those found in salami, sausages, hot dogs, luncheon meats, and bacon. (Previous studies had rarely separated processed meat from unprocessed meat when investigating the relationship between disease and meat eating.) The researchers analyzed twenty studies that included a total of 1,218,380 people from ten countries on four continents (North America, Europe, Asia, and Australia). They found that each 1.8-ounce daily serving of processed meat (about one hot dog or a couple slices of deli meat) was associated with a 42 percent higher risk of developing heart disease. (In contrast, no relationship was found between heart disease and nonprocessed red meat.²⁴)

Although the study didn’t identify which specific ingredients in processed meat could be responsible for the association, many health professionals believe that the high levels of sodium and nitrates might be responsible. “When we looked at average nutrients in unprocessed red and processed meats eaten in the United States, we found that they contained similar average amounts of saturated fat and cholesterol. In contrast, processed meats contained, on average, four times more sodium and 50 percent more nitrate preservatives,” said Renata Micha, a research fellow in the department of epidemiology at the Harvard School of Public Health and lead author of the study. “This suggests that differences in salt and preservatives, rather than fats, might explain the higher risk of heart disease and diabetes seen with processed meats, but not with unprocessed red meats.”²⁵

Fast Action Plan: Cut out processed (e.g., deli) meats.

Dump It: Excessive Omega-6 Fats

Vegetable oils (corn, canola, and soybean) are mostly made up of pro-inflammatory omega-6 fats, and you should reduce (not necessarily eliminate) your consumption of them while increasing your consumption of anti-inflammatory omega-3 fats.

This is the one recommendation that comes with an asterisk. Omega-6 fats, the ones that are most prevalent in vegetable oils, are not in and of themselves “bad.” But they *are* pro-inflammatory, and they need to be balanced by an equal (or near-equal) intake of anti-inflammatory omega-3s. (You can review this information in [chapter 5](#), “The Truth about Fat.”) The optimal ratio of omega-6 to omega-3 in the human diet is no higher than 4 : 1, and many believe the ideal ratio is 1:1. In the average Westernized diet, the ratio is anywhere between 15 : 1 and 25 : 1, which creates a highly inflammatory state in the body. Because heart disease is primarily a disease of inflammation, such a state should be avoided as much as humanly possible.

And by the way, it’s not just the oils you use for cooking that tip the scales into inflammation land. Omega-6 fats are everywhere in the food supply—you can’t swing a rope without hitting a food product loaded with omega-6s. Nearly all processed foods contain them. They’re used almost exclusively in restaurants, for frying, sautéing, and baking, so virtually anything you order from the menu has got a ton of omega-6 fats.

So choose your omega-6 fats carefully and use them sparingly. (The best choices are cold-pressed, unrefined oils—sesame oil is a particularly good choice.) Use highly processed supermarket oils (such as corn oil) infrequently or not at all. When you sauté food, try substituting monounsaturated fats such as olive oil and macadamia nut oil for high omega-6 oils such as canola or soybean. And, above all, increase your intake of omega-3 fats to help balance your intake of omega-6s (see the “Eat This!” section below).

Fast Action Plan: Never use generic processed oils such as Wesson or Crisco. Cut down on corn oil, safflower oil, soybean oil, and canola oil (see Dr. Sinatra’s personal story on canola oil in [chapter 5](#)). Whenever possible,

use olive oil, sesame oil, or macadamia oil. And pay attention to the “Eat This!” section in this chapter on omega-3s.

THE “EAT THIS!” LIST

Both of us are frequently interviewed about the best foods for health. Virtually every reporter either of us has ever spoken with winds up asking, “How much of this food do you need to eat to get its benefits?” It’s a reasonable question, but there’s almost never a perfect answer. We know of no study, for example, that has systematically tested the effects of eating five portions of blueberries a week as opposed to three, or compared eating two portions of salmon per week with eating it daily. Our recommendation is to put these foods in heavy rotation in your diet, enjoying them as frequently as you like.

Here are the foods you want to include in your diet on a regular basis.

Eat This: Wild Alaskan Salmon

Salmon is one of the best sources of anti-inflammatory omega-3s. But not all salmon is created equal. Wild Alaskan salmon is far superior to the farm-raised variety. (According to independent lab tests by the Environmental Working Group, seven out of ten farmed salmon purchased at grocery stores were contaminated with polychlorinated biphenyls [PCBs] at levels high enough to raise health concerns.) Wild salmon is far cleaner, and it has the added benefit of containing one of the most powerful antioxidants on the planet, *astaxanthin*. A 4-ounce serving also contains 462 mg of heart-healthy potassium, the same amount in a medium banana.²⁶

Both of us have been buying our salmon from a wonderful company called Vital Choice for many years. Vital Choice is run by third-generation Alaskan fishermen who are scrupulous about using sustainable fishing and equally scrupulous about testing their fish thoroughly for contaminants and metals. They ship in dry ice, and they have the best fish we’ve ever tasted.

Fast Action Plan: Eat wild salmon twice a week.

Eat This: Berries

All berries are loaded with natural anti-inflammatory properties and natural antioxidants. They’re also very low in sugar. Blueberries contain a

beneficial compound called *pterostilbene*, which helps prevent the deposit of plaque in the arteries and also helps prevent some of the damage caused by oxidized cholesterol.²⁷ Raspberries and strawberries contain another substance, *ellagic acid*, which offers similar protection against oxidized LDL.²⁸ And all berries—blueberries, raspberries, strawberries, and others—contain *anthocyanins*, plant compounds that help lower inflammation (see “Cherries” below).

Fast Action Plan: Eat berries three (or more) times a week.

Eat This: Cherries

Cherries and cherry juice have long been known to be effective against the pain of gout, and scientists believe that the compounds in cherries responsible for this are *anthocyanins*. Anthocyanins act like natural COX-2 inhibitors. “COX” stands for *cyclooxygenase*, which is produced in the body in two forms called COX-1 and COX-2. COX-2 is used for signaling pain and inflammation.

The popularity of arthritis drugs such as Vioxx and Celebrex was based on their unique ability to block the pain and inflammation messages of COX-2 while leaving the non-inflammatory COX-1 alone. Unfortunately, there were some really unpleasant side effects associated with Vioxx, and it was taken off the market. But anthocyanins produce a similar effect with none of the problems of such drugs. Cherries (along with raspberries) have the highest yields of pure anthocyanins. In one study, the COX inhibitory activity of anthocyanins from cherries was comparable to that of ibuprofen and naproxen. Researchers feel that in addition to helping with pain and inflammation, consuming anthocyanins on a regular basis may help lower heart attack and stroke risk.

Fast Action Plan: Eat cherries two (or more) times a week.

Eat This: Grass-Fed Beef

We’re not anti-meat guys, but we are very much against factory-farmed meat. The majority of the meat we consume, unfortunately, is feedlot-raised meat from factory farms. It’s loaded with antibiotics, steroids, and

hormones; it's very high in inflammatory omega-6 fats; and it contains virtually no anti-inflammatory omega-3s.

Grass-fed meat is a whole different “animal.” (Okay, bad pun, sorry, we couldn't resist.) Raised on pasture, it contains less omega-6s plus a fair amount of omega-3s, resulting in a much better omega-6: omega-3 ratio. Grass-fed meat is almost always raised organically, and, in any case, it never has hormones, steroids, or antibiotics. If you eat meat, grass-fed is the only way to go.

Fast Action Plan: Eat only grass-fed meat when you eat meat.

Eat This: Vegetables (and Some Fruit)

No matter what kind of diet you're on—from vegan to Atkins—you can probably benefit from eating more vegetables than you already do. The entire vegetable kingdom is loaded with natural anti-inflammatories, antioxidants, and other plant compounds, such as flavonoids, that are good for your heart.

In two long-running Harvard-based research projects, the Nurses' Health Study and the Health Professionals Follow-up Study, the higher the average daily consumption of vegetables and fruits, the lower the chances of developing cardiovascular disease. Compared with those in the lowest category of fruit and vegetable intake (fewer than one and a half servings daily), those averaging eight or more servings per day were a whopping 30 percent less likely to have had a heart attack or stroke.²⁹

Although all vegetables and fruits probably contributed to this stunning effect, the researchers felt that the most outstanding contributors were the green, leafy veggies (such as spinach and Swiss chard) and the cruciferous ones (broccoli, Brussels sprouts, kale, cabbage, and cauliflower). (In the fruit department, citrus fruits such as oranges, lemons, limes, and grapefruit were particularly protective.³⁰)

When researchers took the Harvard studies mentioned above and combined them with several other long-term studies both in Europe and the United States, they found a similar protective effect. Individuals who ate more than five servings a day of vegetables and fruits had a roughly 20

percent lower risk of coronary heart disease,³¹ and a similar reduction in the risk of stroke.³²

The reason we're not as over-the-top enthusiastic about fruit is that despite its terrific benefits, it still contains sugar, which can be a problem for many folks. For the large number of people whose blood sugar rises when they merely look at a candy bar, unlimited fruit is a bad idea. Low-sugar fruits (such as apples, grapefruit, cherries, berries, and oranges) are fine in moderation. Vegetables, on the other hand, can be virtually unlimited.

Fast Action Plan: Eat 5 to 9 half cup servings of vegetables and fruit a day.

Eat This: Nuts

Although an apple a day may indeed keep the doctor away, the same can also be said of a handful of nuts. People who eat nuts regularly are less likely to have heart attacks or die from heart disease than those who don't. Five large studies—the Adventist Health Study, the Iowa Women's Health Study, the Nurses' Health Study, the Physicians' Health Study, and the CARE Study—have all found a consistent 30 to 50 percent lower risk of heart attacks or heart disease associated with eating nuts several times a week.³³

FIGHT HEART DISEASE WITH FOOD

In a fascinating and much-discussed article that appeared in the December 16, 2004, issue of the *British Medical Journal*, researchers put forth an idea called the *polymeal*.³⁴ They examined all of the research on foods and health to see whether they could put together the ideal meal (the polymeal) that, if you ate it every day, would significantly reduce your risk for cardiovascular disease. They came up with a theoretical meal that, eaten daily, would reduce cardiovascular risk by a staggering 75 percent (there's not a pill in the world that can do that!).

The ingredients of the polymeal?

Wine, fish, almonds, garlic, fruits, vegetables, and dark chocolate.

One of the many reasons for the protective effect of nuts may be an amino acid named *arginine*. Remember our earlier discussion about the endothelium, (the inner lining of the arterial walls)? Arginine has a role in protecting this inner lining, making the arterial walls more pliable and less susceptible to atherogenesis. Arginine is needed to make an important molecule called *nitric oxide*, which helps relax constricted blood vessels and ease blood flow.³⁵

In addition, nuts are a great source of numerous *phytonutrients*—bioactive chemicals found in plants. These compounds have powerful health benefits, not the least of which is their antioxidant activity, which is linked to the prevention of coronary heart disease. And if you're worried about calories, consider this: In the Nurses' Health Study out of Harvard, nut consumption was inversely related to weight gain.³⁶ Several large studies, including the Physicians' Health Study (22,000 men) and the Adventist Health Study (more than 40,000 people), have demonstrated a link between nut eating and a reduction in heart disease.³⁷ Just keep portions reasonable—an ounce or so a day is great.

Fast Action Plan: Eat 1 ounce of nuts five times a week.

Eat This: Beans

Fact number one: Fiber is good. (High-fiber diets have been associated with lower rates of a host of diseases, including heart disease.) Fact number two: We don't get enough of it. (Most health organizations recommend a daily intake of 25 to 38 g daily; the average American gets 11 g.) Fact number three: Beans are a fiber heavyweight.

Case closed.

One study found that one serving of beans on a daily basis lowered the risk of a heart attack by 38 percent.

Regarding heart disease, the big selling point of beans used to be that they lowered cholesterol.³⁸ That's definitely true, but, as you've learned, it's not nearly as important as whether they actually lower *heart disease*. And they do. One study found that one serving of beans on a daily basis lowered the risk of a heart attack by an eyebrow-raising 38 percent!³⁹ Another study found that individuals eating beans and legumes at least four times a week had a 22 percent lower risk of heart disease than individuals consuming beans/legumes less than once a week.⁴⁰

Their high fiber content alone would make beans a top food for the heart, but beans offer a lot more than fiber. The U.S. Department of Agriculture ranking of foods by antioxidant capacity lists small red dried beans as having the highest antioxidant capacity per serving size of any food tested. In fact, of the four top-scoring foods, three were beans (red beans, red kidney beans, and pinto beans). Many bean varieties have a lot of folic acid (especially adzuki beans, lentils, black-eyed peas, and pinto beans). Folic acid is one of the key players in bringing down the inflammatory compound *homocysteine*, itself a risk factor for heart disease.

Fast Action Plan: Eat a serving of beans or lentils at least four times a week. (One serving is $\frac{1}{2}$ cup to 1 cup cooked beans.)

Eat This: Dark Chocolate

Study after study is confirming that plant chemicals in cocoa-rich dark chocolate called *flavanols* can lower blood pressure and reduce inflammation. A 2011 study in the *British Medical Journal* found that high levels of chocolate consumption are associated with a one-third reduction in the risk of developing heart disease. The highest levels of chocolate consumption were associated with a 37 percent reduction in cardiovascular disease and a 29 percent reduction in stroke when compared to the lowest levels.⁴¹

Flavanol-rich cocoa lowers blood pressure.⁴² And the Zutphen Elderly Study of 470 elderly men found that those who ate the most cocoa had literally half the risk of dying from heart disease than men who ate the least.⁴³

Now the thing about chocolate is that all the good stuff is found in the cocoa that it's made from, so you really want high-cocoa chocolate. We're not talking about the candy bars you get at the 7-Eleven here; we're talking about a cocoa-rich chocolate that contains all the flavanols that have been found to be so healthy. White chocolate and milk chocolate have hardly any flavanols to speak of, so it's got to be dark. Many dark chocolate bars will now tell you their cocoa content in percentage form—look for at least 60 percent cocoa. (The higher the cocoa content, the less sweet the bar.)

You'll also find that this kind of chocolate is easy to eat in small quantities—it's not so sweet that it causes you to crave more and more of it, and it's easy to be satisfied with just a square or two, which is all you need for the health benefits.

Fast Action Plan: Eat one to two squares of dark chocolate four to six days a week.

Eat This: Turmeric

Turmeric is the spice that makes curries yellow. It occupies a place of distinction in both Ayurvedic and Chinese medicine, largely because of its phenomenal anti-inflammatory properties. (It also has anticancer activity and is very helpful for the liver.) The active ingredients in turmeric are a group of plant compounds called *curcuminoids* (collectively known as

curcumin). In addition to being anti-inflammatory, curcumin is a powerful antioxidant. Because oxidized LDL is a big player in the cascade that leads to inflammation and heart disease, turmeric's antioxidant properties are a big benefit.

Fast Action Plan: Put turmeric at the front of your spice cabinet and use it often. It goes well on veggies, eggs, sautéed dishes, meats, fish, and poultry.

Eat This: Pomegranate Juice

Pomegranate juice is one of the few “trendy” health foods that actually lives up to its hype. Researchers at the Technion-Israel Institute of Technology in Haifa suggest that long-term consumption of pomegranate juice may help slow aging and protect against heart disease.

In a study published in the *American Journal of Cardiology*, forty-five patients with heart disease drank either 8 ounces of pomegranate juice or 8 ounces of a placebo drink for three months. The pomegranate juice drinkers had significantly less oxygen deficiency to the heart during exercise, suggesting that they had increased blood flow to the heart.

Pomegranate juice has the ability to inhibit the oxidation of LDL cholesterol.⁴⁴ (Remember that LDL cholesterol is only a problem when it's oxidized!) And an impressive number of studies have demonstrated a beneficial effect of pomegranate juice on cardiovascular health, including one that showed 30 percent reduced arterial plaque.⁴⁵ Pomegranate juice also enhances the activity of nitric oxide, a molecule essential for cardiovascular health.⁴⁶

One caution: Avoid “juice blends” and “juice cocktails,” because these have much less pomegranate juice in them and much more sugar. We like pure pomegranate juices such as Just Pomegranate, which are admittedly expensive but contain absolutely nothing but pure pomegranate juice. Another popular brand we like a lot is Pom Wonderful.

Fast Action Plan: Put pomegranate juice in “heavy rotation” on your menu: 4 to 8 ounces a day, or as often as you like.

Eat This: Red Wine

For years, it was believed that the reason the French could “get away” with eating high-fat foods—while still having remarkably lower rates of heart disease than Americans—was because of their regular consumption of red wine, which contains numerous compounds that protect the heart. Chief among these is *resveratrol*, a polyphenol (plant compound) that’s found in the skins of dark grapes and is highly concentrated in red wine. Resveratrol is a potent antioxidant that can prevent harmful elements in the body from attacking healthy cells. Red wine has been shown to be cardioprotective in quite a number of studies.⁴⁷ And resveratrol isn’t the only reason. Other compounds in red wine such as flavonoids inhibit the oxidation of LDL cholesterol, which is pretty darn important because oxidized LDL cholesterol initiates and intensifies the inflammatory process.⁴⁸ Red wine also limits the tendency of compounds in the blood to clot and increases HDL cholesterol to boot.⁴⁹ Interestingly, in one study, moderate consumption of red wine was associated with lower levels of three markers we told you about earlier: CRP, fibrinogen, and interleukin-6.⁵⁰ It’s hard to think of a more heart-healthy drink.

Worth noting: The dark side of alcohol is well known, and we don’t have to recount it here. If you’re not a drinker, please don’t start because of the benefits of red wine. Not everyone can handle alcohol, and if you suspect you’re someone who doesn’t do well with it, for goodness’ sake, don’t drink it! (With all the talk about how the wine-drinking French have the lowest rates of heart disease in western Europe, it’s frequently forgotten that they also have the highest rates of liver cirrhosis!) The key to enjoying wine’s beneficial effects is moderate consumption, defined as about two glasses a day for men and about one a day for women, about three to four times a week. Also worth mentioning is that alcohol increases the risk for breast cancer in women who aren’t consuming enough folic acid, so make sure you’re getting at least 400 mg of folic acid a day through food or supplementation.

Fast Action Plan: If you are a drinker, have a glass of red wine with dinner. (If you’re not, don’t start!)

Eat This: Green Tea

Apart from water, tea is probably the most consumed beverage in the world, and it's also one of the healthiest. That's because it's absolutely loaded with protective plant-based chemicals known as *polyphenols*. Green tea in particular has gotten a ton of attention in the media, largely for the anti-cancer action of one of its compounds, *epigallocatechin gallate* (EGCG).

But green tea also contributes to cardiovascular health. Although much has been written about its cholesterol-lowering effect, we find it much more interesting that green tea lowers fibrinogen, a substance in the body that can cause clots and strokes. In an article in the journal *Circulation* titled “Effects of Green Tea Intake on the Development of Coronary Artery Disease,” researchers from the department of medicine at Chiba Hokusoh Hospital, Nippon Medical School, Chiba, Japan, concluded that “the more green tea patients consume, the less likely they are to have coronary artery disease.”⁵¹

Worth knowing: Just because green tea gets the lion's share of attention from health writers doesn't mean there's not great stuff in other teas, such as black, oolong, white, and yerba mate. At Boston University's School of Medicine, Joseph Vita, M.D., conducted a study in which sixty-six men either drank four cups of black tea a day or took a placebo. The researchers showed that drinking black tea can help reverse an abnormal functioning of blood vessels that can contribute to stroke or heart attack. Best of all, improvement in the functioning of the blood vessels was visible within two hours of drinking just one cup of black tea!⁵²

“What we found was that if you take a group of people with heart disease who have abnormal blood vessel function to begin with and asked them to drink tea, their blood vessels improved,” said Vita.⁵³

Fast Action Plan: Remember, any form of tea contains caffeine, so drink in moderation. Make a big pitcher of green tea and keep it in the fridge. Drink it in the earlier part of the day, up to two glasses.

Eat This: Olive Oil

Olive oil is the primary fat used in the Mediterranean area and the one most associated with what's been called the Mediterranean diet. (There is no single “Mediterranean diet,” but all variations of it contain high amounts of

fish, fruits, vegetables, nuts, wine, and olive oil.) There are countless studies on the Mediterranean diet and heart health and virtually all of them show enormous benefits for the heart and the brain. These studies have left olive oil with an unimpeachable reputation as one of the healthiest fats for the heart.

Research in the *Archives of Internal Medicine* concluded that greater adherence to the traditional Mediterranean diet (including plenty of olive oil and other monounsaturated fats such as nuts and avocados) was associated with significant reduction in mortality among people who had been diagnosed with heart disease.⁵⁴ Another study in the same journal compared two groups of people with high blood pressure.⁵⁵ One group was given sunflower oil, a typical high omega-6 oil used in Western diets, and one group was given the good stuff: extra-virgin olive oil. The olive oil decreased the second group's blood pressure by a significant amount; it also decreased their need for blood pressure meds by a whopping 48 percent. As the English might say, "Not too shabby."

Like red wine and green tea, olive oil contains polyphenols that are anti-inflammatory and act as powerful antioxidants. (Researchers have isolated one in particular, *oleocanthal*, which acts similarly to ibuprofen.⁵⁶) Because so many of these polyphenols have significant health benefits, some people believe that the fat in olive oil may not be the only reason olive oil is so darn healthy. They think that the main health benefits of olive oil come from the fact that it is a delivery system for these powerful polyphenols. Either way, the stuff is great, and you should make it a part of your heart-healthy diet.

Worth knowing: All olive oil is not created equal. Unfortunately, commercial manufacturers, trying to ride the health hype on olive oil, have rushed to market all kinds of imitation and inferior products that say "olive oil" on them but are highly processed and refined and have questionable benefits. That's why you want "extra-virgin" olive oil, which is the least processed, the most like what you'd get if you walked around barefoot in barrels of olives. It's made without the use of heat, hot water, or solvents, and it is left unfiltered. (The first pressing produces the best stuff, known as "extra-virgin.")

Once you begin machine harvesting and processing with very high heat, you start damaging the delicate compounds in olive oil responsible for all

those great health benefits. The antioxidant and anti-inflammatory polyphenols are water soluble and can be washed away with factory processing. That's one reason that factory-produced olive oil has a shorter shelf life—no antioxidants to protect it. Real olive oil—the extra-virgin kind, made with care and love and the absence of high heat and harsh chemicals—lasts for years.

Fast Action Plan: Switch to extra-virgin olive oil. Use it for salad dressing, low-heat stir-fries, and sautées.

Eat this: Garlic

Garlic is a global remedy. More than 1,200 (and counting) pharmacological studies have been done on garlic, and the findings are pretty impressive. In addition to lowering lipids and preventing blood coagulation, it has antihypertensive, antioxidant, antimicrobial, and antiviral properties. Garlic has been shown to lower triglyceride levels. It can also reduce plaque, making it a powerful agent for cardiovascular health.

In one study, subjects receiving 900 mg of garlic powder for four years in a randomized, double-blinded, placebo-controlled study had a regression in their plaque volume of 2.6 percent; meanwhile, a matched group of subjects given a placebo (an inert substance) saw their plaque increase over the same time period by 15.6 percent!⁵⁷

One of the active ingredients in garlic—*allicin*—also has significant antiplatelet activity. That means it helps prevent platelets in the blood from sticking together. To understand just how important that is, consider that many heart attacks and strokes are caused by spontaneous clots in the blood vessels. The anticoagulant effect of garlic is an important health benefit.

Worth knowing: The preparation of garlic is critical for it to release its health-providing benefits. If for any reason you had the impulse to swallow a garlic clove whole, not much would happen. The garlic clove has to be crushed or chopped—the more finely the better—for the compounds in it to mix together to create *allicin*, the active ingredient responsible for the health benefits. Allicin starts degrading immediately after it's produced, so the fresher it is when you use it, the better. (Microwaving destroys it completely.) Garlic experts advise crushing a little raw garlic and

combining it with cooked food. If you add it to food you're sautéing, do it toward the end so the allicin is freshest.

Fast Action Plan: Start cooking with garlic.

THE “HIDDEN RISK FACTORS” FOR HEART DISEASE

Everyone reading this book needs to know this: You can prevent and even heal heart disease through diet, exercise, and/or nutritional supplements.

But if you’re interested in doing that—and we’re pretty sure you are, or you wouldn’t be reading this—diet, exercise, and supplements are only a part of the picture. The many hidden emotional and psychological risk factors that are hardly ever addressed by conventional medicine are equally important—and sometimes even more so. They include suppressed anger, rage, the loss of love (what Dr. Sinatra calls “heartbreak”), and the emotional isolation that results from lack of intimacy with other people; we’ve touched on some of this in the previous chapter on stress.

Opening your heart to your feelings and learning how to express them in a healthy way will do far more for your heart and your overall health than you might imagine. Here are some specific ways you can accomplish this.

Breathe Deeply

When people are subjected to chronic stress, they oftentimes become tense and rigid. They take shallow breaths. Improper breathing can, over the course of time, result in actual physical changes in the body, such as a more rigid upper body, including the chest and shoulders. High chest breathing tends to be rapid and shallow and is frequently associated with emotional upset, physical tension, or ordinary mental stress. Slow, rhythmic, deep abdominal breathing, however, is physiologically more suited to the body and has the added benefit of allowing a greater intake of oxygen.

Proper breathing has been the subject of many stress-management programs. It’s the first place you start when you learn to meditate, and it’s a principle focus of yoga. In Gestalt psychotherapy, deep breathing is used as a vehicle to loosen up the energy of the chest and to free emotions.

A more prolonged form of deep breathing is meditation, which has an impressive amount of research showing that it lowers blood pressure effectively. Cardiologist Herbert Benson, M.D., has been doing pioneering research on meditation and deep breathing for decades. An associate

professor of medicine at Harvard Medical School and founder of the Benson-Henry Institute for Mind Body Medicine at Massachusetts General Hospital, he coined the term “the Relaxation Response” to refer to a physical state of deep rest that changes the physical and emotional responses to stress. And it’s all based on deep breathing and calming the mind.

Benson was able to show time and again that the relaxation response decreases the heart rate, lowers blood pressure, slows the rate of breathing, and relaxes the muscles. It also increases levels of nitric oxide—a molecule that’s important for circulation and improved blood flow. Tai chi, meditation, yoga, and mindfulness are all able to elicit the relaxation response.

According to the Benson-Henry Institute, between 60 and 90 percent of all doctor visits are for complaints related to, or affected by, stress. “Scores of diseases and conditions are either caused or made worse by stress,” Benson has said. “These include anxiety, mild or moderate depression, anger, hostility, hot flashes of menopause, infertility, PMS, high blood pressure, and heart attacks. Every one can be caused by stress or exacerbated by it. And to the extent that that’s the case, the relaxation response is helpful.” ⁵⁸

HOW TO DO “THE RELAXATION RESPONSE”

Allow ten to twenty minutes to try this simple technique:

- Sit quietly in a comfortable position.
- Close your eyes.
- Deeply relax all your muscles beginning at your feet and progressing up to your face. Keep them relaxed.
- Breathe through your nose. Become aware of your breathing. As you breathe out, say the word *one* silently to yourself. For example, breathe in . . . out, (one), in . . . out (one), etc. Breathe easily and naturally.
- Continue for ten to twenty minutes.
- You may open your eyes to check the time, but don’t use an alarm. When you finish, sit quietly for several minutes at first with your eyes closed and later with your eyes open. Don’t stand for a few minutes.

“Don’t worry about whether you are successful in achieving a deep level of relaxation. Maintain a passive attitude and permit relaxation to occur at its own pace. When distracting thoughts occur, try to ignore them by not dwelling upon them and return to repeating *one*.”

—From *The Relaxation Response* by Herbert Benson, M.D., used with permission

NOTE: Try not to do this within a couple hours of eating. According to Benson, the digestive process seems to interfere with eliciting the relaxation response.

See the sidebar on how you can do the relaxation response.

How Crying and Laughing Can Help

Next to love, crying is perhaps the most healing activity for the heart. It frees the heart of muscular tension and rigidity. Sobbing enhances oxygen

delivery. Man is the only primate able to weep for emotional reasons. Weeping is nature's way of releasing the pain of heartbreak and preventing death. Any expression of feeling will help to heal your heart. Despite what we're taught, it's not weak to show your feelings. In fact, it's far healthier than "stuffing" your feelings and seething silently.

Laughing is a way of experiencing strong feelings, just as crying is. (In fact, strenuous laughter often turns into tears.) When you laugh fully, breathing increases, freeing up the rigidity in the chest, diaphragm, and even deep down in the psoas muscles. As a spontaneous release of energy, laughter has the potential to be extremely therapeutic.

Laughing Your Way to Health

Over the course of his lifetime, Norman Cousins, the legendary journalist and editor of the *Saturday Evening Post*, suffered from a number of serious medical conditions, including heart disease and ankylosing spondylitis, a disease characterized by chronic inflammation along the axial skeleton. At one point, doctors gave him little hope of surviving. He ignored their doomsaying and developed his own program for recovery that involved love, hope, faith, and, courtesy of the Marx Brothers films he loved to watch, an awful lot of laughter.

Although he eventually died of heart failure at age seventy-five, Cousins lived far longer than his doctors predicted, a full thirty-six years after first being diagnosed with heart disease. (Cousins also did research on the biochemistry of human emotions at the School of Medicine at the University of California, Los Angeles, and wrote two important books on emotion, healing, and illness—*Anatomy of an Illness* and *The Healing Heart*.)

Sex: The Advantages of Intimacy

Have you ever wondered why some elderly people look much younger than their stated age while some younger people look so much older? This observation was studied by a Russian gerontologist who examined 15,000 individuals over the age of eighty in provinces of the former Soviet Union. He found several common denominators or markers for longevity. People who lived the longest reported working outdoors, high levels of physical activity, and a diet high in vegetables, fruits, and fresh whole grains. But

several of the common denominators involved relationships, intimacy, and sexuality.

Many of these individuals continued to have an active sex life well into their eighties and nineties. And why not? Aging couples who are committed to one another's pleasure can adapt sexually to the aging process. On an emotional level, sexuality provides a sense of security, connectedness, and emotional intimacy. When sexuality is an expression of love, the energies of the partners can fuse in harmony like two tuning forks vibrating with the same frequency. Feelings of warmth, connectedness, and emotional intimacy can help open our hearts.

EXPRESSING EMOTIONS (ESPECIALLY FOR MEN!)

Showing and expressing feelings can be a huge challenge for some people, particularly men. But getting in touch with your feelings doesn't have to be embarrassing at all. You don't have to get up in front of some encounter group and spill your guts to strangers. All it may take is a pencil and paper.

A writing exercise developed by social psychologist James Pennebaker has been tested in dozens of studies in which subjects were assigned to write about either mundane activities, such as running errands, or personal traumas. The technique is pure simplicity. You write your deepest thoughts and emotions about any event, situation, person, or even trauma for about fifteen minutes on four consecutive nights. Pennebaker has found that people who do this simple, private exercise show improvements in immune system functioning, are less likely to visit doctors, get better grades in school, and miss fewer days of work.⁵⁹

The Power of Touch and Massage

Touch therapy or massage appears to be associated with a decreased heart rate, decreased blood pressure, and increased endorphin release, resulting in an increased sense of relaxation and heightened well-being. In humans, massage can be considered a tranquilizer with absolutely no side effects!

Remember the parasympathetic (slowing down) and the sympathetic (speeding up) nervous systems? Massage activates the parasympathetic system and provides a nice, healing balance to the typical sympathetic overdrive experienced by type-A, coronary-prone individuals.

Play

Play is one of the most healing things you can do for your heart health and your emotional well-being. And most adults have no idea how to do it. Sure, we talk about “playing” tennis or golf, but sports are different—though enjoyable, they’re not healing because they involve performance, competition, and the need to win! (Just ask Dr. Jonny how he feels after losing a tennis match!)

Play is totally different. True play is spontaneous and has no agenda, rules, or regulations, or even a desired outcome. When we play, we are totally free. That is, we do things solely for joy and pleasure. When we play, we become totally absorbed in what we are doing; we are taken out of our heads (and down into our bodies). Time stops for us.

Think of how completely absorbed five- or six-year-olds become when they’re painting a picture. Within minutes, nothing else matters to them but the colors, the feel of the brush on the paper, the way the paint drips and blobs and runs, the way the colors mix, and how closely they can match the picture with the image in their minds. Being carried away by their imaginations and getting their inspirations down on paper is, for a short time, the single most important thing in the world to them. Everything else falls away—worries, fears, wants, needs, hunger—and is replaced by a sense of total involvement, excitement, satisfaction, and gratification.

If you can play even partially this way, it can completely cut you free from stress and worry and help heal your mind and heart. Because of this nearly miraculous benefit of play, we encourage you to play like children. If, like most adults, you’ve forgotten how, observe children and see what they do.

Remember, play has no outcome, no goal. You need to play for play’s sake alone, and, when you play, try to bring out the little child inside you. Once you connect with your inner child—believe us, we all have one—it will bring you to another level of healing.

Final Words

Foods can fuel your heart, supplements can support it, and exercise can strengthen it. But never neglect the “hidden” emotional and psychological risk factors that contribute to the development of heart disease as surely as smoking, a high-sugar diet, stress, high blood pressure, and lack of exercise do.

Building and maintaining strong emotional connections with other people is one of the best stress-management strategies on the planet. It’s also one of the best ways to keep your heart healthy and your soul nourished. Next to exercise, it’s the closest thing we have to a panacea. It also makes life a lot more rich, a lot more fun, and a lot more gratifying.

Enjoy the journey.

GLOSSARY

Adenosine triphosphate (ATP)—the body’s energy molecule.

Adrenal glands—endocrine glands that sit on top of the kidneys. They secrete stress hormones such as cortisol and adrenaline.

Adrenaline (also known as epinephrine)—a hormone secreted by the adrenal glands that increases heart rate, constricts blood vessels, and participates in the “fight or flight” response.

Advanced glycation end products (AGEs)—the end products of a reaction in which a sugar molecule bonds to a protein molecule. AGEs are implicated in many chronic diseases such as diabetes and heart disease.

All-cause mortality—death from any cause whatsoever.

Allicin—the major biologically active component of garlic, responsible for its broad spectrum of antibacterial activity.

Alpha-linolenic acid (ALA)—a plant-based omega-3 fatty acid that helps reduce inflammation and is found in flaxseed, chia seeds, hemp, and walnuts.

Amino acids—molecules that link together to form proteins.

Angina—chest pain or discomfort produced when the heart doesn’t get enough blood.

Anthocyanins—compounds found in plants, especially berries, that have powerful antioxidant properties. Anthocyanins provide the pigments responsible for the rich colors of berries.

Arteriosclerosis—general term for any kind of hardening or stiffening of the arteries.

Artery—a blood vessel that carries blood away from the heart.

Astaxanthin—a powerful antioxidant found primarily in wild salmon and krill. It's responsible for salmon's pink-red color.

Atherogenic—capable of producing plaque in the arteries.

Atherosclerosis—a condition in which the arteries thicken, the walls become inflamed, material builds up, and plaque is formed. Commonly referred to as “hardening of the arteries.”

Atom—the smallest component of an element having the chemical properties of the element.

Beta blocker—a class of drugs used for various indications such as cardiac arrhythmias and hypertension. It diminishes the effects of stress hormones such as adrenaline.

Bifurcation—to separate into two parts or branches, as when the main stem of a blood vessel divides to become two smaller vessels.

Bile acids—a complex fluid found in the bile of mammals that aids in fat absorption. Bile acids are produced from cholesterol in the liver and stored in the gallbladder.

Blood clot (also known as a thrombus)—blood clots form when there is damage to the lining of a blood vessel. Normal clotting is an important mechanism in helping the body repair injured blood vessels. When unneeded blood clots form, however, this can have potentially serious consequences.

Blood pressure—the pressure exerted against the walls of the blood vessels by circulating blood.

Calcification (as in the arteries)—the process by which calcium builds up in soft tissue, including arteries and heart valves, causing it to harden.

Carbohydrates—one of the three “macronutrients” or classes of food (the others are protein and fat). Carbohydrates include sugars and starch.

Cardiac ischemia (also known as myocardial ischemia)—a decrease in blood flow that reduces your heart's oxygen supply. It can damage your heart muscle.

Cholesterol (includes serum cholesterol)—a waxy sterol that is an essential component of cell membranes. (A sterol is a particular type of

fat.) It's the principal sterol synthesized by animals and is important for the manufacture of sex hormones, vitamin D, and bile acids.

Coenzyme Q₁₀ (CoQ₁₀)—a vitamin-like substance found in every cell in the body; essential for the manufacture of the body's energy molecule, ATP; a powerful antioxidant; approved since 1974 in Japan, where it is used for heart failure. It is significantly depleted by statin drugs.

Conjugated linoleic acid (CLA)—a “good” trans fat found in the meat and milk of grass-fed animals. Much research has shown that it has anticancer properties and may also help with body composition (reduction in body fat).

Control group—a group in a scientific experiment that is treated identically to the experimental group in every way except that it's not given the drug or treatment being tested. In drug tests, the control group gets a placebo. The effects of the drug or treatment are measured in the experimental group, which is then compared to the control group.

Cortisol—a steroid hormone produced by the adrenal gland. It is the primary “stress hormone” in the body

COX-2 inhibitors—a class of compounds (often drugs) that inhibit enzymes in the body called COX (cyclooxygenase). COX-1 maintains the normal lining of the stomach while COX-2 increases in response to inflammation. COX-2 inhibitors reduce inflammation while leaving COX-1 alone.

C-reactive protein—protein in the blood used as a systemic measure of inflammation.

Cytokines—inflammatory chemicals produced by a variety of cells in the body, including those in the adipose (fat) tissue.

D-alpha tocopherol—one of eight forms of vitamin E.

Diabetes, type 1—an autoimmune disease that results in the destruction of the insulin-producing cells in the pancreas. Type 1 diabetics don't produce enough insulin, and the disease is typically fatal unless treated with exogenous insulin (either by injection, inhalation, or insulin pumps).

Diabetes, type 2—a chronic condition in which the cells “ignore” insulin (see *insulin resistance*), usually resulting in dangerously high blood sugar and insulin levels. Ninety to 95 percent of diabetics have this type of diabetes, which is a lifestyle-related disease.

Diet–heart hypothesis—the idea that saturated fat and dietary cholesterol cause or contribute to heart disease.

DL-alpha tocopherol—a synthetic form of vitamin E.

Docosahexaenoic acid (DHA)—an omega-3 fatty acid found primarily in fish. It is particularly important for the brain.

Dolichols—important for the synthesis of glycoproteins, which in turn are important for emotions, cell identification, cell messaging, and immune defense. Statin drugs reduce them, because dolichols are produced by the same pathway that produces cholesterol and is interrupted by statin drugs. Reduced bioavailability of dolichols can affect every cellular process in the body.

Double-blind study—a study in which neither the subjects nor the experimenters know which subjects are getting an active drug and which subjects are getting a placebo. Double-blind studies are believed to minimize the effect of experimenter and patient expectations.

D-ribose—molecule made in the body’s cells and used for cellular function.

Eicosanoids—mini hormones that control metabolic processes in the body; also called prostaglandins.

Eicosapentaenoic acid (EPA)—an important omega-3 fatty acid found primarily in fish. It is particularly important for the heart.

Electrons—tiny subatomic particles that carry a negative electric charge and surround the nuclei of atoms.

Ellagic acid—a natural antioxidant found in many vegetables and fruits, particularly raspberries, strawberries, and pomegranates. It is being investigated for its anticancer properties.

Endocrinology—the study of hormones and what they do.

Endothelial dysfunction (ED)—dysfunction of the cells that line the inner surface of all blood vessels. A major feature of endothelial dysfunction

is the inability of the arteries to dilate (open) fully. ED contributes to several diseases, including diabetes, and it is always associated with heart disease.

Endothelium—the thin layer of cells that lines the inner surface of blood vessels.

Enzyme—a complex protein that speeds the rate at which certain chemical processes take place.

Epinephrine (also known as adrenaline)—an important stress hormone released by the adrenal glands.

Estrogen—family of hormones that perform about four hundred functions in the human body; produced primarily in the ovaries and adrenal glands; known as the “female hormone” but present in both women and men.

Farnesyl-PP—an intermediate in the HMG-CoA pathway.

Fat—one of the three major classes of nutrients known as “macronutrients” (the others being protein and carbohydrates). It is made up of smaller units called fatty acids.

Fatty acids—the building blocks of fat.

Fiber—indigestible component of food; associated with lower risks of heart disease, diabetes, obesity, and cancer.

Fibrates—a class of drugs used for lowering cholesterol. They also lower triglycerides.

Fibrin—a protein essential for the clotting of blood.

Fibrinogen—a protein that is converted to fibrin during the blood-clotting process.

Flavanols—a group of plant pigments, including the anthocyanins, that are beneficial to health.

Flavonoids—plant compounds that have antioxidant and anti-inflammatory activity.

Folic acid—a water-soluble B vitamin needed for proper development of the human body and to help the body make healthy new cells. Folic acid

is the synthetic (man-made) form of folate, found naturally in some foods.

Free radicals—destructive molecules in the body; can harm cells and DNA by producing “oxidative damage.”

Fructose—fruit sugar, found naturally in honey, berries, fruits, and most root vegetables. Table sugar is half glucose, half fructose. The most damaging of the sugars when taken in concentrated forms such as sugar, high-fructose corn syrup, or agave nectar. Causes insulin resistance, fatty liver, and elevated triglycerides.

Geranyl-PP—a product of the condensation of dimethallyl-pp and isopentyl-pp.

Glucagon—the “sister” hormone of insulin, made in the pancreas. Increases when blood sugar levels are low. Helps counteract the effects of insulin.

Glucocorticoids—a class of steroid hormones produced by the adrenal glands. Cortisol is the most important glucocorticoid.

Glucose—a simple sugar and component of most carbohydrates. Table sugar is 50 percent glucose. It is measured in the blood as blood glucose.

Glycation—the result of the bonding of a protein molecule with a sugar molecule. It is also known as nonenzymatic glycosylation.

Glycemic Index—measure of how much a portion, specifically 50g, of a given food raises blood sugar.

Hemochromatosis—a disorder that results in too much iron being absorbed from the gastrointestinal tract.

High-density lipoprotein (HDL)—a complex of lipids and proteins that transports cholesterol in the blood and is often thought of as the “good” cholesterol.

High-fructose corn syrup—a sweetener made by processing corn syrup to increase the level of fructose.

HMG-CoA reductase—an enzyme that plays a central role in the production of cholesterol in the liver.

Homeostasis—derived from the Greek, meaning “remaining stable” or “remaining the same.” A relatively stable state of equilibrium.

Homocysteine—an amino acid found in the blood, high levels of which increase the chance of heart disease, stroke, osteoporosis, and Alzheimer’s. Homocysteine can be lowered with folic acid, vitamin B₆, and vitamin B₁₂.

Hormones—chemical messengers that travel in the bloodstream and affect sexual function, growth, development, mood, and many different metabolic processes.

Hydrogenated or partially hydrogenated oil—the process of adding hydrogen to vegetable oil is called hydrogenation. It makes the oil less likely to spoil but also creates trans fat, the most damaging of all the fatty acids.

Hypertension—high blood pressure.

Hyperviscosity—increased thickness of the blood.

Inflammation, acute—a tissue response to injury, usually of a sudden onset. Examples include injuries to the knee or back, abscesses, and skin outbreaks. Classical signs include pain, heat, redness, and swelling.

Inflammation, chronic—prolonged and persistent inflammation that often flies beneath the pain radar. It is a critical component of nearly all degenerative diseases. Chronic, persistent inflammation of the vascular walls is a major cause of heart disease.

Insulin—fat-storing hormone that, if raised high enough, long enough, and frequently enough, contributes to diabetes, heart disease, and aging.

Insulin resistance—the condition in which the cells stop “listening” to insulin, resulting in high blood sugar and high insulin. Insulin resistance is associated with metabolic syndrome and type 2 diabetes.

Intermediate-density lipoprotein (IDL)—one of five major groups of lipoproteins that transport different types of molecules, including cholesterol, through the bloodstream.

Isopentyl pyrophosphate (IPP)—an intermediate in the HMG-CoA pathway.

Keys, Ancel (1904–2004)—an American researcher and scientist whose Seven Countries Study appeared to show that serum cholesterol was strongly related to coronary heart disease. He persuaded many Americans—and mainstream health organizations—to adopt and endorse a low-fat diet.

L-carnitine—a vitamin-like compound that escorts fatty acids into the mitochondria of the cells, where it can be “burned” for energy.

Left ventricular hypertrophy—enlargement (hypertrophy) of the muscle tissue that makes up the wall of the heart’s main pumping chamber (the left ventricle).

Lipid core—an important component of “vulnerable plaque” (plaque prone to rupture). Approximately 40 percent of vulnerable plaque is composed of the lipid core.

Lipid rafts—regions of cell membranes that are involved in intracellular signaling pathways. They are particularly rich in cholesterol.

Lipoproteins—structures that transport fats, especially cholesterol and triglycerides, from place to place within the bloodstream.

Low-density lipoprotein (LDL)—one of five major groups of lipoproteins that transport different types of molecules, including cholesterol, through the bloodstream. It’s popularly known as the “bad” cholesterol.

Lumbrokinase (also known as *Boluo*)—an extract from earthworms that lowers blood viscosity (thickness), helps thin the blood, and helps prevent clots by breaking down fibrinogen.

Macrophages—white blood cells that devour foreign invaders such as fungi and bacteria.

Magnesium—a mineral that helps lower high blood pressure.

Maladaptation—faulty or inadequate adaptation; a trait that has become more harmful than helpful.

Mediterranean diet—the general name given to diets from the Mediterranean Sea areas that emphasize fruits, vegetables, whole grains, olive oil, beans, nuts, fish, and small amounts of red meat.

Meta-analysis—a “study of studies” that combines data from several studies that address a set of related research hypotheses; a statistical procedure for combining data from multiple studies.

Metabolic syndrome—the name for a group of risk factors that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes. It’s also known as prediabetes, and it’s characterized by insulin resistance, high triglycerides, abdominal fat, high blood pressure, low HDL cholesterol, and high blood sugar.

Mevalonate pathway (HMG-CoA reductase pathway)—the biochemical pathway that produces cholesterol as well as coenzyme Q₁₀ and other important compounds such as dolichols.

Mitochondria—the power stations in every cell where energy is produced.

Monocytes—a type of white blood cell that attacks bacteria or viruses.

Monounsaturated fatty acids—fats central to the Mediterranean diet; associated with lower rates of heart disease; found in nuts and olive oil; also called omega-9s.

Myocardial infarction—a heart attack.

Nattokinase—an enzyme extracted from the Japanese food called natto (fermented soybeans). A natural blood thinner and clot buster (similar in effect to lumbrokinase).

Neurotransmitters—chemicals produced mainly in the brain that transmit information; examples are serotonin, dopamine, and epinephrine.

Niacin (nicotinic acid, vitamin B₃)—often used to lower LDL cholesterol and/or raise HDL.

Nuclear factor kappa B (NF-κB)—a “smoke sensor” that detects dangerous threats, such as free radicals and infectious agents, and responds by unleashing inflammatory responses in chronic diseases. It is produced by the mevalonate pathway and inhibited by statin drugs.

Nutraceutical—combination of the word “nutrition” and “pharmaceutical”; a supplement that provides health benefits.

Omega-3 fatty acids—a class of polyunsaturated fatty acids that have strong anti-inflammatory properties and are important for the brain and

the heart.

Omega-6 fatty acids—a class of polyunsaturated fats found in vegetable oils. They are pro-inflammatory, especially when not balanced with enough omega-3s.

Oxidation (also known as *oxidative damage*)—the damage to skin, organs, and arteries caused by free radicals; along with inflammation, one of the initiators of heart disease; implicated in many other diseases as well.

Oxidative stress—the damage done to cells by free radicals of oxygen molecules; another term for oxidation or oxidative damage.

Oxytocin—a chemical often called the “bonding” hormone that is released during breastfeeding and sex. It can elicit the urge to connect to others.

Pantethine—biologically active form of vitamin B₅; often used for lowering cholesterol.

Pattern A—desirable distribution of LDL particles in which the big, fluffy, innocuous particles predominate.

Pattern B—undesirable distribution of LDL particles in which the small, atherogenic particles predominate.

Placebo-controlled study—a way of testing in a scientific experiment in which one group (or more) gets the treatment or the drug and another group (the control group) gets an inert substance (placebo).

Plaque (atherosclerotic plaque)—a deposit of fat and other substances that accumulate in the lining of arterial walls.

Platelet—a cell-like particle in the blood that is an important part of blood clotting.

Polyphenols—large class of plant chemicals, many of which have significant health benefits.

Polyunsaturated fatty acids—large class of fatty acids with many members, including both the omega-3s and the omega-6s; found in vegetable oils, nuts, and fish.

Prenylated proteins—proteins anchored to membranes.

Primary prevention—treatment to prevent a first heart attack.

Progesterone—an important hormone secreted by the female reproductive system.

Protein—one of the three “macronutrients” or classes of food (the others are carbohydrates and fat).

Pterostilbene—a chemical related to resveratrol and found in blueberries and grapes; may have significant health benefits.

Randomized study—a study in which subjects are randomly assigned to either treatment or control groups.

Risk reduction, absolute—the actual amount of risk reduction from taking a certain drug or eating a certain diet. For example, if 3 percent of all subjects could be expected to die over the course of a decade but only 2 percent of subjects taking a drug *actually* died over the course of the same decade, the absolute risk reduction is 1 percent.

Risk reduction, relative—risk reduction expressed as the percent difference between expected and observed. In the above example, the difference between 3 percent expected death and 2 percent observed death would be expressed as a 33 percent reduction in *relative risk*, a much more impressive number but very misleading.

Saturated fatty acids—a fatty acid in which there are no double bonds. Saturated fats are found primarily in animal foods and are solid at room temperature.

Secondary prevention—treatment to prevent a subsequent heart attack in patients who have already suffered one or more heart attacks.

Selenoproteins—a class of proteins that contain the essential mineral selenium.

Seven Countries Study—a study by Ancel Keys purporting to show that cholesterol and fat in the diet are the prime causes of heart disease. It was later criticized for bias and poor methodology.

Squalene—a metabolic precursor of sterols.

Statins—a class of drugs used to lower cholesterol. Also known as HMG-reductase inhibitors.

Stress, acute—a kind of stress that is usually short-term; it can be thrilling and exciting, like a run down a challenging ski slope, or it can be unpleasant, like anger or a headache.

Stress, chronic—the grinding stress that wears people down day after day, year after year. It is considered a contributing factor in heart disease.

Sugar—a sweet crystalline substance obtained from various plants, especially sugar beet and sugar cane.

Testosterone—the major male sexual hormone belonging to the steroid family; produced in the testes of males but also produced (in smaller amounts) by females in the ovaries.

Thrombus—a blood clot formed within the vascular system, impeding blood flow.

Tocopherols—a class of four closely related chemical compounds that are part of the vitamin E family.

Tocotrienols—a class of four potent antioxidants and heart-healthy nutrients that are part of the vitamin E family.

Total cholesterol—the sum total of all “types” of cholesterol measured in the blood. Includes LDL and HDL cholesterol, as well as lesser known VLDL and IDL; given as one number on a blood test.

Trans fatty acids—a special kind of fat formed when liquid fats are made into solid fats by the addition of hydrogen atoms; partially hydrogenated or hydrogenated vegetable oils.

Triglycerides—main form of fat found in the body and in the diet and nearly always measured on a standard blood test; high levels increase the risk for heart disease and are a feature of metabolic syndrome.

Vasodilate—the dilation (widening) of blood vessels from the relaxation of the muscular wall of the vessels, resulting in lowered blood pressure.

Very low-density lipoprotein (VLDL)—one of five types of lipoproteins, packages that transport substances such as cholesterol and triglycerides throughout the bloodstream.

Voodoo death—term coined by physiologist Walter Cannon, M.D., that refers to the phenomenon of sudden death brought on by strong

emotional shock, stress, or fear.

Yudkin, John (1910–1995)—British physiologist and scientist; pioneer researcher examining the link between sugar and degenerative disease; became internationally known for his book on sugar, *Pure, White and Deadly*.

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CHAPTER 9

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- * Trans fats are a special category.
- * Mevacor, a statin drug, was actually introduced in 1987, but statins didn't become popular until the 1990s.
- * Randomized, double-blind studies are the “gold standard” of these kinds of trials and considered much more reliable than those that are either nonrandomized, nonblinded, or both.
- * When the results of JUPITER came out, the stock of AstraZeneca—the company that makes Crestor—shot up by double digits.
- * A form of vitamin injection administered slowly over the course of ten to fifteen minutes.

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